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(54) Title: NOVEL CHOLECYSTOKININ ANTAGONISTS, THEIR PREPARATION AND THERAPEUTIC USE

(57) Abstract

Novel cholecystokinin antagonists useful as agents in the treatment of obesity, hypersecretion of gastric acid in the gut, gastrin-dependent tumors, or as antipsychotics are disclosed. Further, the compounds are antianxiety agents and antiulcer agents. They are agents useful for preventing the response to the withdrawal from chronic treatment with use of nicotine, diazepam, alcohol, cocaine, coffee, or opioids. The compounds of the invention are also useful in treating and/or preventing panic. Also disclosed are pharmaceutical compositions and methods of treatment using the antagonists as well as processes for preparing them and novel intermediates useful in their preparation. An additional feature of the invention is the use of the subject compounds in diagnostic compositions.

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NOVEL CHOLECYSTOKININ ANTAGONISTS,
THEIR PREPARATION AND THERAPEUTIC USE

CROSS-REFERENCE TO RELATED APPLICATION

5

This application is a continuation-in-part of
United States Serial Number 07/576,628, filed
August 31, 1990.

10   BACKGROUND OF THE INVENTION

Agents acting at central cholecystokinin (CCK)
receptors may induce satiety (Schick, Yaksh, and Go,
Regulatory Peptides 14:277-291, 1986). They are also
15   expected to act as analgesics (Hill, Hughes, and
Pittaway, Neuropharmacology 26:289-300, 1987), and as
anticonvulsants (MacVicar, Kerrin, and Davison, Brain
Research 406:130-135, 1987).

Reduced levels of CCK-peptides have been found in
20   the brains of schizophrenic patients compared with
controls (Roberts, Ferrier, Lee, Crow, Johnstone,
Owens, Bacarese-Hamilton, McGregor, O'Shaughnessey,
Polak, and Bloom, Brain Research 288:199-211, 1983).
It has been proposed that changes in the activity of
25   CCK neurones projecting to the nucleus accumbens may
play a role in schizophrenic processes by influencing
dopaminergic function (Totterdell and Smith,
Neuroscience 19:181-192, 1986). This is consistent
with numerous reports that CCK peptides modulate
30   dopaminergic function in the basal ganglia and
particularly the nucleus accumbens (Weiss, Tanzer, and
Ettenberg, Pharmacology, Biochemistry and Behaviour
30:309-317, 1988; Schneider, Allpert, and Iversen,
Peptides 4:749-753, 1983). It may therefore be
35   expected that agents modifying CCK receptor activity

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may have therapeutic value in conditions associated
with disturbed function of central dopaminergic
function such as schizophrenia and Parkinson's
disease.

5   CCK and gastrin peptides share a common carboxy
terminal pentapeptide sequence and CCK peptides can
bind to the gastrin receptor of the stomach mucosa and
elicit acid secretion in many species including human
(Konturek, Gastrointestinal Hormones, Ch. 23, pp 529-
10   564, 1980, ed. G. B. J. Glass, Raven Press, NY).
Antagonists of the CCK-B receptor would also be
expected to be antagonists at the stomach gastrin
receptor and this would also be of value for
conditions involving excessive acid secretion.

15   CCK and gastrin peptides have trophic effects on
the pancreas and various tissues of the gastro-
intestinal tract (Johnson, ibid., pp 507-527), actions
which are associated with increased DNA and RNA
synthesis. Moreover, gastrin secreting cells are
20   associated with certain gastrointestinal tumors as in
the Zollinger-Ellison syndrome (Stadil, ibid., pp 729-
739), and some colorectal tumors may also be
gastrin/CCK dependent (Singh, Walker, Townsend, and
Thompson, Cancer Research 46:1612, 1986; Smith, J. P.,
25   Gastroenterology 95:1541, 1988). Antagonists of
CCK/gastrin receptors could therefore be of
therapeutic value as antitumor agents.

        The CCK peptides are widely distributed in
various organs of the body including the
30   gastrointestinal tract, endocrine glands, and the
nerves of the peripheral and central nervous systems.
Various biologically active forms have been identified
including a 33-amino acid hormone and various
carboxyl-terminus fragments of this peptide (e.g., the

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octapeptide CCK26-33 and the tetrapeptide CCK30-33).
(G. J. Dockray, Br. Med. Bull. 38(3):253-258, 1982).
        The various CCK peptides are thought to be
involved in the control of smooth muscle

5   contractility, exocrine and endocrine gland secretion,
sensory nerve transmission, and numerous brain
functions. Administration of the native peptides
cause gall bladder contraction, amylase secretion,
excitation of central neurons, inhibition of feeding,

10   anticonvulsive actions and other behavioral effects.
(Cholecystokinin: Isolation, Structure and Functions,
G. B. J. Glass, Ed., Raven Press, New York, 1980,
pp 169-221; J. E. Morley, Life Sciences 27:355-368,
1980; Cholecystokinin in the Nervous System,

15   J. de Belleroche and G. J. Dockray, Ed., Ellis
Horwood, Chichester, England, 1984, pp 110-127.)
        The high concentrations of CCK peptides in many
brain areas also indicate major brain functions for
these peptides (G. .J. Dockray, Br. Med. Bull.

20   38(3):253-258, 1982). The most abundant form of brain
CCK found is CCK26-33, although small quantities of
CCK30-33 exist (Rehfeld and Gotterman, J. Neurochem.
32:1339-1341, 1979). The role of central nervous
system CCK is not known with certainty, but it has

25   been implicated in the control of feeding (Della-Fera
and Baile, Science 206:471-473, 1979).
        Currently available appetite suppressant drugs
either act peripherally, by increasing energy
expenditure (such as thyroxine), or in some other

30   manner (such as the biguanides), or act by exerting a
central effect on appetite or satiety.
        Centrally acting appetite suppressants either
potentiate central catecholamine pathways and tend to
be stimulants (for example, amphetamine), or influence

35   serotonergic pathways (for example, fenfluramine).

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Other forms of drug therapy include bulking agents
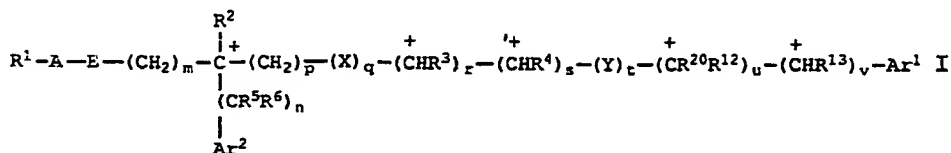which act by filling the stomach, thereby inducing a
"feeling" of satiety.

5   CCK is known to be present in some cortical
interneurones which also contain gamma-aminobutyric
acid (GABA) (H. Demeulemeester et al, _J. Neuroscience_
8:988-1000, 1988). Agents that modify GABA action may
have utility as anxiolytic or hypnotic agents
(S. C. Harvey, _The Pharmacological Basis of_

10   _Therapeutics_ (7th ed.) 1985, pp 339-371, MacMillan).
Thus, agents which modify CCK action may have parallel
anxiolytic or hypnotic activities. The role of CCK in
anxiety is disclosed in _TIPS_ 11:271-273, 1990.

15

SUMMARY OF THE INVENTION

The invention relates to novel compounds of the
formula

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$$R^1-A-E-(CH_2)_m-\overset{\overset{\displaystyle R^2}{|}}{\underset{\underset{\displaystyle Ar^2}{\overset{\displaystyle |}{(CR^5R^6)_n}}}{C}}\overset{+}{-}(CH_2)\overline{_p}-(X)_q-\overset{+}{(CHR^3)_r}-\overset{'+}{(CHR^4)_s}-(Y)_t-\overset{+}{(CR^{20}R^{12})_u}-\overset{+}{(CHR^{13})_v}-Ar^1 \quad I$$

25   and the pharmaceutically acceptable salts thereof
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^{12}, R^{13}, R^{20}, A, X, Y,
E, Ar^1, Ar^2, n, m, p, q, r, s, t, u, and v are as
defined hereinbelow.

In commonly owned copending applications

30   07/576,308, 07/576,296, 07/576,315, 07/576,024, and
07/576,297 filed on August 31, 1990, by Horwell, et

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al, the disclosures of which are incorporated herein
by reference, CCK antagonists are disclosed.

In the continuation-in-part applications of the
above applications also commonly owned and copending

5   _____, _____, _____, _____,
and _____ filed on even date herewith by Horwell,
et al, the disclosures of which are incorporated
herein by reference, CCK antagonists are disclosed.
In like manner, the present invention relates to a

10   pharmaceutical composition containing an effective
amount of a compound according to formula I in
combination with a pharmaceutically acceptable carrier
in unit dosage form effective for appetite
suppression.

15   The compounds are also useful as anxiolytics,
antipsychotics, especially for treating schizophrenic
behavior, as agents in treating disorders of the
extrapyramidal motor system, as agents for blocking
the trophic and growth stimulating actions of CCK and

20   gastrin, and as agents for treating gastrointestinal
motility.

Compounds of the invention are also useful as
analgesics, and they potentiate the effect of
morphine. They can be used as an adjunct to morphine

25   and other opioids in the treatment of severe pain such
as cancer pain, and reduce the dosage of morphine
required in the treatment of pain where morphine is
contraindicated.

An additional use for compounds of the invention

30   is that a suitable radiolabeled isotope gives an agent
suitable for treatment of gastrin dependent tumors
such as those found in colonic cancers. I-125
radiolabeled compounds of the invention can also be
used as diagnostic agents by localization of gastrin

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and CCK-B receptors in both peripheral and central
tissue.

The invention further relates to a method of
appetite suppression in mammals which comprises
administering an amount effective to suppress appetite
of the composition described above to a mammal in need
of such treatment.

The invention also relates to a pharmaceutical
composition for reducing gastric acid secretion
containing an effective amount of a compound of
formula I in combination with a pharmaceutically
acceptable carrier in unit dosage form effective for
reducing gastric acid secretion.

The invention also relates to a method for
reducing gastric acid secretion in mammals which
comprises administering an amount effective for
gastric acid secretion reduction of the composition
described above to a mammal in need of such treatment.

The invention also relates to a pharmaceutical
composition containing an effective amount of a
compound of formula I in combination with a
pharmaceutically acceptable carrier in unit dosage
form effective for reducing anxiety.

The invention also relates to a method for
reducing anxiety in mammals which comprises
administering an amount effective for anxiety
reduction of the composition described above to a
mammal in need of such treatment.

The invention also relates to a pharmaceutical
composition containing an effective amount of a
compound of formula I in combination with a
pharmaceutically acceptable carrier in unit dosage
form effective for treating gastrointestinal ulcers.

The invention further relates to a method for
treating gastrointestinal ulcers in mammals which

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comprises administering an amount effective for
gastrointestinal ulcer treatment of the composition as
described above to a mammal in need of such treatment.

The invention also relates to a pharmaceutical
5   composition containing an effective amount of a
compound of formula I in combination with a pharma-
ceutically acceptable carrier in unit dosage form
effective for treating psychosis, i.e., schizophrenia.

The invention further relates to a method for
10   treating psychosis in mammals which comprises
administering an amount effective for treating
psychoses of a composition as described above to a
mammal in need of such treatment.

The invention also relates to pharmaceutical
15   compositions effective for stimulating or blocking CCK
or gastrin receptors, for altering the activity of
brain neurons, for schizophrenia, for treating
disorders of the extrapyramidal motor system, for
blocking the trophic and growth stimulating actions of
20   CCK and gastrin, and for treating gastrointestinal
motility.

The invention also relates to a pharmaceutical
composition for preventing the withdrawal response
produced by chronic treatment for abuse of drugs or
25   alcohol.

The invention further relates to a method for
treating the withdrawal response produced by
withdrawal from chronic treatment or withdrawal from
abuse of drugs or alcohol. Such drugs include
30   benzodiazepines, especially diazepam, cocaine,
alcohol, and nicotine. Withdrawal symptoms are treated
by administration of an effective withdrawal treating
amount of a compound of the invention.

The invention also relates to a pharmaceutical
35   composition containing an effective amount of a

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compound of formula I in combination with a
pharmaceutically acceptable carrier in unit dosage
form effective for treating and/or preventing panic.

The invention also relates to a method for
5   treating and/or preventing panic in mammals which
comprises administering an amount effective for panic
treatment and/or prevention of the composition
described above to a mammal in need of such treatment.

The invention further relates to the use of the
10   compounds of formula I to prepare pharmaceutical and
diagnostic compositions for the treatment and
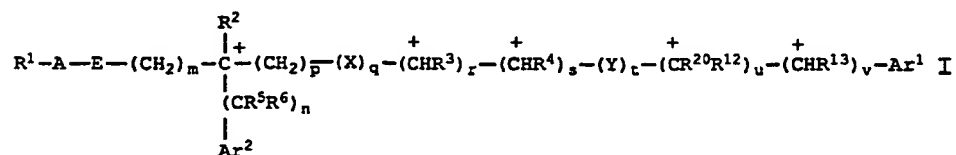diagnosis of the conditions described above.

The invention further provides processes for the
preparation of compounds of formula I.

15   The invention further provides novel
intermediates useful in the preparation of compounds
of formula I and also provides processes for the
preparation of the intermediates.

20   DETAILED DESCRIPTION

The compounds of the present invention are
represented by the formula

25

$$R^1-A-E-(CH_2)_m-\overset{\overset{R^2}{|}}{\underset{\underset{Ar^2}{|}}{\underset{(CR^5R^6)_n}{\overset{+}{C}}}}-(CH_2)_{\overline{p}}(X)_q-(CHR^3)_r\overset{+}{-}(CHR^4)_s-(Y)_t\overset{+}{-}(CR^{20}R^{12})_u-(CHR^{13})_v\overset{+}{-}Ar^1 \quad I$$

30

or a pharmaceutically acceptable salt thereof wherein:
R^1 is a cyclo or polycycloalkyl hydrocarbon or mono-
       or polyheterocycle moiety (wherein the hetero
35   atom(s) can be N, O, and/or S of from 3 to

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12 carbon atoms with from 0 to 4 substituents
each independently selected from a straight or
branched alkyl of from 1 to 6 carbon atoms,
halogen, CN, OR*, SR*, CO_2R*, CF_3, NR^5R^6, or
$(CH_2)_nOR^5$ wherein R*, R^5, and R^6 are each
independently hydrogen or a straight or branched
alkyl of from 1 to about 6 carbon atoms;

m, n, p, q, r, s, t, u, and v are each independently
an integer of from 0 to 6 with the proviso that
q, r, and s are not all 1 when m, p, t, u, and v
are all 0 except when X is not $CONR^9$ or A-E is
not $(CH_2)_nCONH-$, $-SO_2NH-$, $-S(O)NH-$, $-NHCONH$,
$-(CH_2)_n-OCO-NH-SCONH-$, $-O(CH_2)_nCO-$ or $-HC=CHCONH-$
wherein n is as above,

A is a bond,

O,

S,

NR*,

$-(CH_2)_nCO-Z$,

$-SO_2-Z$,

$-SO-Z$,

$-S-Z$,

$-NHCO-Z$,

$$-(CH_2)_n-O\overset{\overset{O}{\|}}{C}-Z,$$

$-SCO-Z$,

$-O-(CH_2)_nCO-Z$,

$-HC=CHCO-Z$,

wherein Z is a bond, oxygen, sulphur, or $-NR*-$
wherein R* is as defined above;

E is a bond,

an amino acid residue,

$-(CHR^3)_r-$,

$-(CHR^3)_r-(CHR^4)_s-$,

$-CONH-$,

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-NHCO-,

-OCO-,

-COO-,

$-CH_2N(R^3)-$,

-CH₂O-,

-CH₂S-,

-C=C-,

$$\overset{\displaystyle S}{\underset{\displaystyle -C-NR^3,}{\|}}$$

$-SO_2NR^3-$,

$-NR^3SO_2-$,
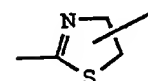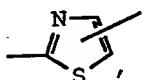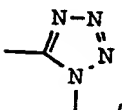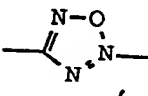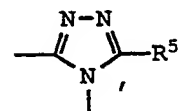
-NHCONH-

wherein r and s are independently as defined above;

R^2 and R^{20} are each independently hydrogen, a straight or branched alkyl of from 1 to 6 carbon atoms, $-HC=CH_2$, $-C\equiv CH$, $-(CH_2)_nCH=CH_2$, $-(CH_2)_nC\equiv CH$, $-(CH_2)_nAr^1$, $-(CH_2)_nAr^2$, $-(CH_2)_nOR^*$, $-(CH_2)_nOAr$,

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$-(CH_2)_nCO_2R^*$, $-(CH_2)_nNR^5R^6$ wherein n, R^*, R^5, and R^6 are as defined above, and Ar^1 and Ar^2 are as defined below;

X and Y are each independently:

$-CONH-$,

$-CONR^9$,

$-NHCO-$,

$-OCO-$,

$-COO-$,

$-CH_2N(R^3)-$,

$-CH_2O-$,

$-CH_2S-$,

$-OCH_2-$,

$-SCH_2-$,

$-C=C-$,

$$\overset{S}{\underset{\|}{-C}}-NR^3,$$

$$\overset{S}{\underset{\|}{-NR_3-C}}-,$$

$-SO_2NR^3-$,

$-NR^3SO_2-$,

$-NHCONH-$,

$-CH(OR^*)CH_2-$,

$-COCH_2-$,

$-CH_2CO-$,

$-NR^3CH_2-$,

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wherein Q is O, S, or NR^9;

R^3 and R^4 are each independently the same as R^2 or

$-(CH_2)_{n'}-B-D$ wherein n' is an integer of from 0 to 3;

B is a bond,

$-OCO(CH_2)_n-$,

$-O(CH_2)_n-$,

$-NHCO(CH_2)_n-$,

$-CONH(CH_2)_n-$,

$-NHCOCH=CH-$,

$-COO(CH_2)_n-$,

$-CO(CH_2)_n-$,

$-SO(CH_2)_n-$,

$-S(CH_2)_n-$,

$-SO_2(CH_2)_n-$,

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$$NHCO-\underset{\underset{R^7}{|}}{C}=\underset{\underset{R^8}{|}}{C}-,$$

$$NHCO-\underset{\underset{R^7}{|}}{\overset{\overset{H}{|}}{C}}-\underset{\underset{R^8}{|}}{\overset{\overset{H}{|}}{C}}-\ ,$$

$$CONH-\underset{\underset{R^7}{|}}{C}=\underset{\underset{R^8}{|}}{C}-,\ or$$

$$CONH-\underset{\underset{R^7}{|}}{\overset{\overset{H}{|}}{C}}-\underset{\underset{R^8}{|}}{\overset{\overset{H}{|}}{C}}-,$$
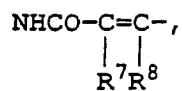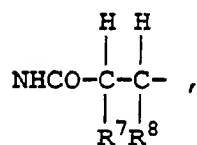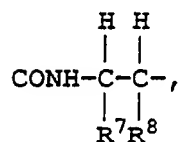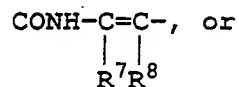
wherein R^7 and R^8 are each independently selected from hydrogen and R^2 or together form a ring $(CH_2)_m$ wherein m is an integer of from 1 to 5,

D is $-COOR*$,

$-CH_2OR*$,

$-CHR^2OR*$,

$-CH_2SR*$,

$-CHR^2SR*$,

$-CONR^5R^6$,

$-CN$,

$-NR^5R^6$,

$-OH$,

$-H$, and acid replacements such as
   tetrazole;

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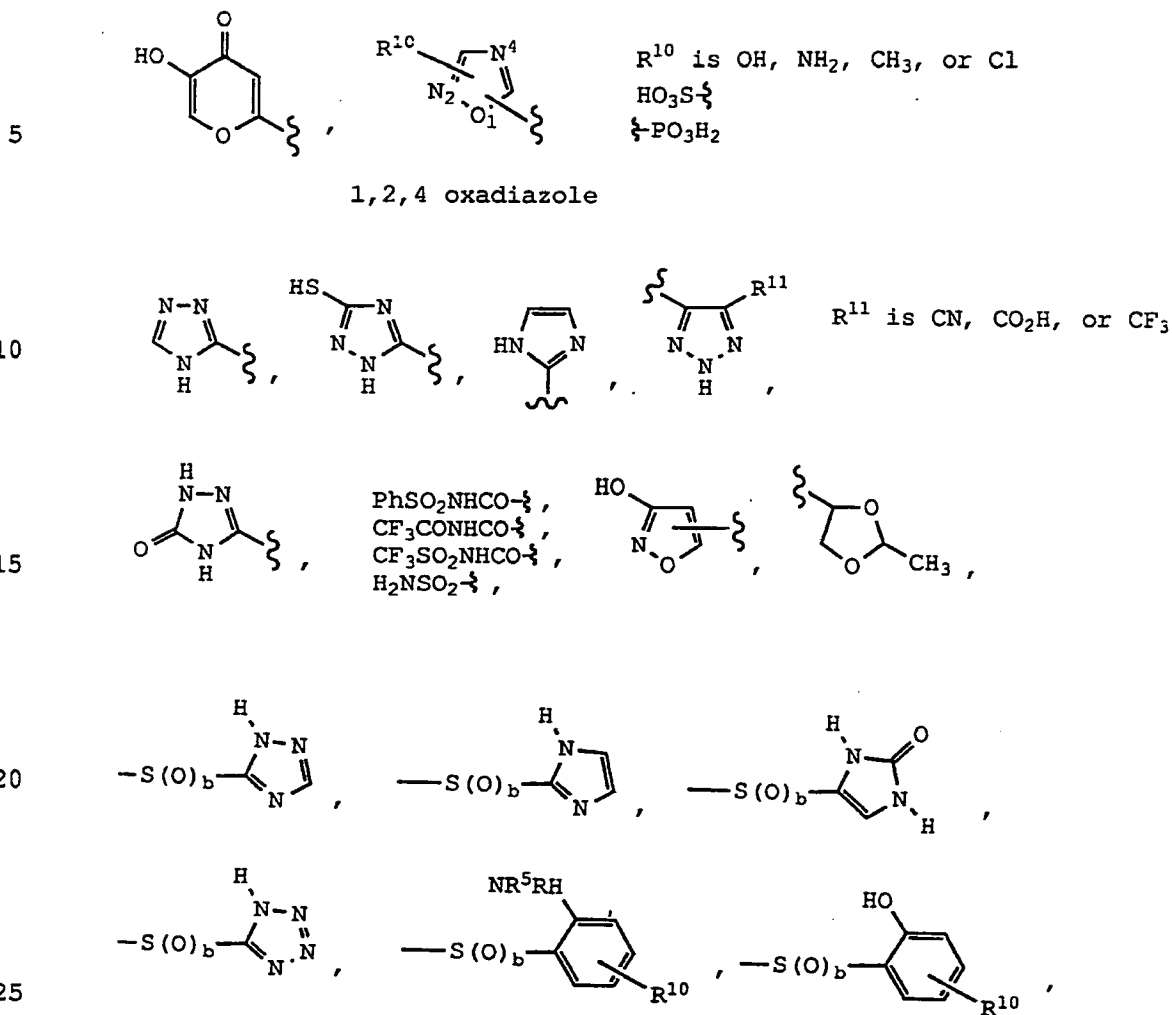
R^{10} is OH, NH$_2$, CH$_3$, or Cl

HO$_3$S-

-PO$_3$H$_2$

1,2,4 oxadiazole

R^{11} is CN, CO$_2$H, or CF$_3$

PhSO$_2$NHCO- ,
CF$_3$CONHCO- ,
CF$_3$SO$_2$NHCO- ,
H$_2$NSO$_2$- ,

wherein b is an integer of from 0 to 2,

wherein R*, R^2, R^5, and R^6 are as defined above; R^9 is H, or a straight or branched alkyl of from one to six carbon atoms, -(CH$_2$)$_n$CO$_2$R*, (CH$_2$)$_n$OAr', (CH$_2$)$_n$Ar', (CH$_2$)$_n$NR^{5}R^6, wherein n, R*, R^5, and R^6 are as defined above or taken from R^3 and Ar' is taken from Ar as defined below;

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R^{12} and R^{13} are each independently hydrogen or taken together form a double bond, or are $-(CH_2)_n-B-D$ as defined above; and

Ar^1 and Ar^2 are each independently a mono- or polycyclic unsubstituted or substituted carbo- or heterocyclic aromatic or carbo- or heteroaromatic moiety; and

Preferred Ar^1 is substituted phenyl, fused aryl, heterocycle, fused heterocycle, or perhydroaryl.

Preferred Ar^1 is 2 or 3-thienyl, 2 or 3-furanyl, 2, 3 or 4-pyridinyl or an unsubstituted or substituted benzene ring

wherein E^1 and F are each independently hydrogen, fluorine, chlorine, bromine, iodine, methyl, methoxy, trifluoromethyl, nitro, hydroxy, NH_2, OCF_3, $NHCOCH_2CH_2OH$, or $CH_2CH_2CO_2H$.

Preferred cycloalkyl or polycycloalkyl substituents have from six to ten carbon atoms.

Preferred compounds of the instant invention are those wherein cycloalkyl is a substituted or unsubstituted
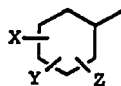
and wherein polycycloalkyl is selected from

wherein W, X, Y, and Z are each independently
hydrogen, a straight or branched alkyl of from one to
six carbon atoms, CF_3, NR^5R^6, $-(CH_2)_nCO_2R^*$, or CN, F,
Cl, Br, OR^*, SR^*, wherein R^* is hydrogen or a straight
or branched alkyl of from one to six carbon atoms and
R^5 and R^6 are as defined above and n is an integer of
from 1 to 3.

Preferred mono- or polyheterocyclic moieties
wherein the heteroatom can be W, O, and/or mono- and
polycyclic hydrocarbons include compounds wherein

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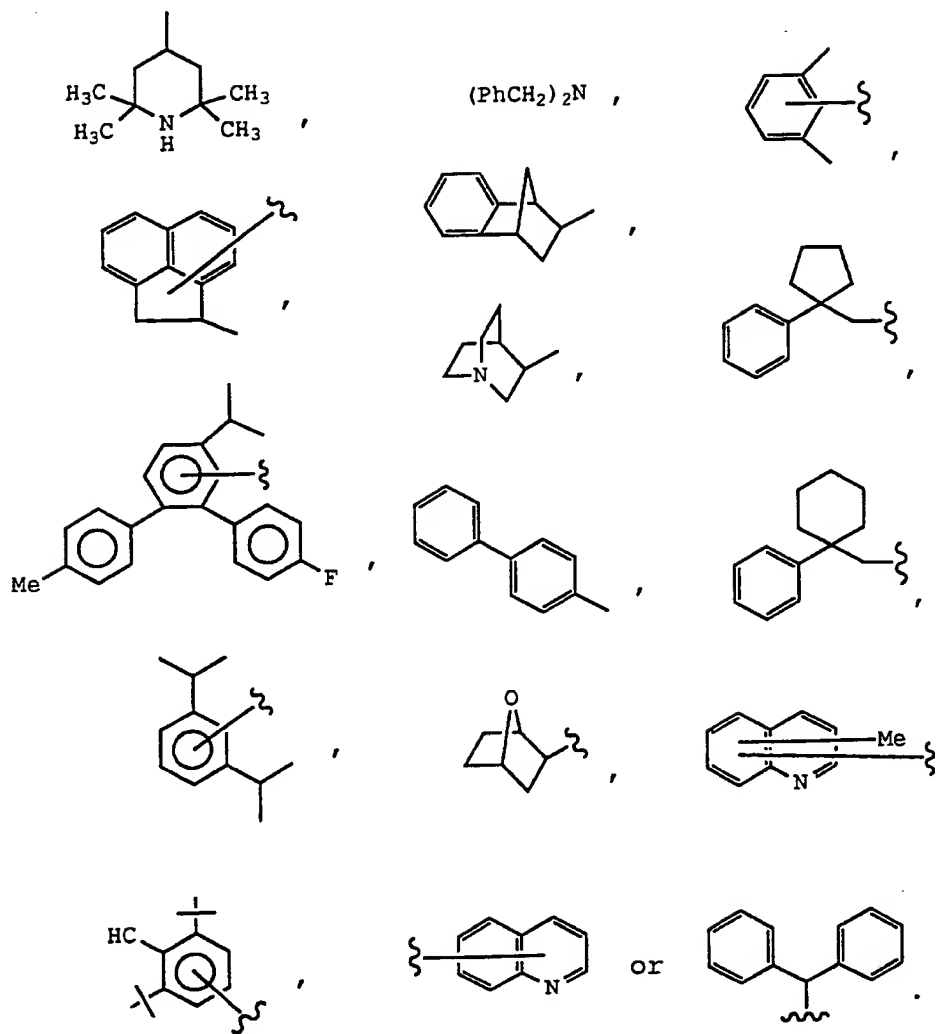
R^1 is

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Other preferred compounds of the instant invention are those wherein

R^1 is 2-adamantyl or 1-(S)-2-endobornyl;

A is -NHCO-, -OCO-, -SO$_2$-, -S(=O)- or -CH$_2$CO-;

R^2 is -CH$_3$, -CH$_2$CO$_2$CH$_3$ or -CH$_2$C≡CH;

R^3 is -(CH$_2$)$_n$-B-D or H; and

R^4 is -(CH$_2$)$_n'$-B-D or H.

More preferred compounds of the instant invention are those wherein

R^1 is 2-adamantyl or 1-(S)-2-endobornyl,

$$A \text{ is } -O-\overset{\overset{\textstyle O}{\|}}{C}-,$$

R^2 is -CH$_3$;

R^3 is H, -CH$_2$OH, -CH$_2$OCOCH$_2$CH$_2$CO$_2$H,

   -CH$_2$OCOCH=CHCO$_2$H, -CH$_2$CO$_2$H-, -CH$_2$SCH$_2$CO$_2$H-,

   -CH$_2$SCH$_2$CH$_2$CO$_2$H-, -CH$_2$NHCOCH$_2$CH$_2$CO$_2$H, or

   -CH$_2$NHCOCH=CHCO$_2$H and

R^4 is H, -NHCOCH$_2$CH$_2$CO$_2$H ([D] configuration) or

   -NHCOCH=CHCO$_2$H ([D] configuration).

The D and the L configurations are possible at the chiral centers and are included in the scope of the invention:

1. Preferred is when R^2 is -CH$_3$ [D] configuration;

2. Preferred is when R^3 is -CH$_2$OCOCH$_2$CH$_2$CO$_2$H or -CH$_2$NHCOCH$_2$CH$_2$CO$_2$H with the [D] configuration at the Trp ∝-carbon atom and the [L] configuration at the Phe-∝-carbon atom; and

3. Preferred is when R^4 is -NHCOCH$_2$CH$_2$CO$_2$H[D] configuration or NHCOCH=CHCO$_2$H[D] configuration with the [D] configuration at the Trp ∝-carbon atom.

Most preferred compounds of the instant invention are:

Carbamic acid, [2-[[1-(hydroxymethyl)-2-phenylethyl]amino]-1-(1H-indol-3-ylmethyl)ethyl]-, tricyclo[3.3.1.1^{3,7}]dec-2-yl ester, [S-(R*,S*)]-,

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Carbamic acid, [2-[[1-(hydroxymethyl)-2-phenylethyl]amino]-1-(1H-indol-3-ylmethyl)ethyl-, tricyclo[3.3.1.1^{3,7}]dec-2-yl ester, [S-(R*,R*)]-,

5   Tricyclo[3.3.1.1^{3,7}]dec-2-yl[1-[[[1-hydroxy-methyl)-2-phenylethyl]carbonyl]amino]-2-(1H-indol-3-yl)ethyl]carbamate,

Carbamic acid, [2-[(2-hydroxy-2-phenylethyl)-amino]-1-(1H-indol-3-ylmethyl)-1-methylethyl]-, tricyclo[3.3.1.1^{3,7}]dec-2-yl ester (hydroxy center is
10   RS, other center is R),

Carbamic acid, [2-[[1-(hydroxymethyl)-2-phenyl-ethyl]amino]-1-(1H-indol-3-ylmethyl)-1-methylethyl]-, tricyclo[3.3.1.1^{3,7}]dec-2-yl ester, [R-(R*,S*)]-, 4-methylbenzenesulfonate (1:1) (salt),

15   Benzenepropanol, ß-[[2-(1H-indol-3-yl)-2-[[tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]amino]-propyl]amino]-, acetate (ester), [R-(R*,S*)]-, 4-methylbenzenesulfonate (1:1) (salt),

Carbamic acid, [[2-[acetyl[1-(hydroxymethyl)-2-
20   phenylethyl]amino]-1-(1H-indol-3-ylmethyl)-1-methyl]-ethyl]-, tricyclo[3.3.1.1^{3,7}]dec-2-yl ester, [R-(R*,S*)]-,

5,13-Dioxo-2,8-diazatetradec-10-enoic acid, 3-(1H-indol-3-ylmethyl)-3-methyl-4,9,12-trioxo-7-
25   phenyl-, tricyclo[3.3.1.1^{3,7}]dec-2-yl ester, [S-(R*,S*)]-,

5,13-Dioxo-2,8-diazatetradecanoic acid, 3-(1H-indol-3-ylmethyl)-3-methyl-4,9,12-trioxo-7-phenyl-, tricyclo[3.3.1.1^{3,7}]dec-2-yl ester, [R-(R*,R*)]-,

30   Carbamic acid, [1-(1H-indol-3-ylmethyl)-1-methyl-2-[(1-oxo-4-phenylbutyl)amino]ethyl]-, tricyclo]3.3.1.1^{3,7}]dec-2-yl ester (R)-,

Carbamic acid, [2-(benzoylamino)-1-(1H-indol-3-ylmethyl)-1-methylethyl]-, tricyclo[3.3.1.1^{3,7}]dec-2-yl
35   ester, (R)-,

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Carbamic acid, [1-(1H-indol-3-ylmethyl)-1-methyl-
2-[(1-oxo-3-phenylpropyl)amino]ethyl]-,
tricyclo[3.3.1.1^{3,7}]dec-2-yl ester, (R)-,

Carbamic acid, [1-(1H-indol-3-ylmethyl)-1-methyl-
2-[(2-phenylacetyl)amino]ethyl]-, tricyclo-
[3.3.1.1^{3,7}]dec-2-yl ester, (R)-,

Carbamic acid, [2-[[3-[[1-(hydroxymethyl)-2-
phenylethyl]amino]-3-oxopropyl]amino]-1-(1H-indol-3-
ylmethyl)-1-methyl-2-oxoethyl]-, [R,(R*,S*)]-,

Carbamic acid, [1-(1H-indol-3-ylmethyl)-2-[[3-
[[1-(hydroxymethyl)-2-phenylethyl]amino]-3-
oxopropyl]amino]-1-methyl-2-oxoethyl]-, tricyclo-
[3.3.1.1^{3,7}]dec-2-yl ester, [S-(R*,R*)]-,

D-Phenylalaninamide, α-methyl-N-
[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-D-
tryptophyl-ß-alanyl-,

L-Phenylalaninamide, α-methyl-N-
[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-D-
tryptophyl-ß-alanyl-,

L-Phenylalaninamide, α-methyl-N-
[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-L-
tryptophyl-ß-alanyl-,

D-Phenylalaninamide, α-methyl-N-
[tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-L-
tryptophyl-ß-alanyl-,

12-Oxo-2,5,9-triazatridecanoic acid, 3-(1H-indol-
3-ylmethyl)-3-methyl-4,8,11-trioxo-10-(phenylmethyl)-,
tricyclo[3.3.1.1^{3,7}]dec-2-yl ester, [R,(R*,R*)]-,

L-Phenylalanine, N-[N-[α-methyl-N-
[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-D-
tryptophyl]-ß-alanyl]-, phenylmethyl ester,

Propanoic acid, 2-[[3-[[3-(1H-indol-3-yl)-2-
methyl-1-oxo-2-[[(tricyclo[3.3.1.1^{3,7}]dec-2-
yloxy)carbonyl]amino]propyl]amino]-1-oxopropyl]-
amino]-3-phenyl-, phenylmethyl ester, [S-(R*,R*)]-,

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D-Phenylalanine, N-[N-[α-methyl-N-
[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-D-
tryptophyl]-ß-alanyl]-,

L-Phenylalanine, N-[N-[α-methyl-N-
[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-D-
tryptophyl]-ß-alanyl]-,

L-Phenylalanine, N-[N-[α-methyl-N-
[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-L-
tryptophyl]-ß-alanyl]-,

Benzenepropanoic acid, α-[[3-[[3-[(1H-indol-3-
yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.1^{3,7}]dec-2-
yloxy)carbonyl]amino]propyl]amino]-1-oxopropyl]-
amino]-, [S-(R*,S*)]-,

Glycine, N-[2-methyl-N-[(tricyclo[3.3.1.1^{3,7}]dec-
2-yloxy)carbonyl]-D-tryptophyl]-, phenylmethyl ester,

Carbamic acid, [3-(1H-indol-3-ylmethyl)-2,5-
dioxo-1-(2-phenylethyl)-3-pyrrolidinyl]-,
tricyclo[3.3.1.1^{3,7}]dec-2-yl ester, (±)-,

Carbamic acid, [1-(1H-imidazol-4-ylmethyl)-1-
methyl-2-oxo-2-[(2-phenylethyl)amino]ethyl]-, 1,1-
dimethylethyl ester, (±)-,

Carbamic acid, [3-(1H-indol-3-yl)-1-methyl-1-
[[(2-phenylethyl)amino]carbonyl]propyl]-,
tricyclo[3.3.1.1^{3,7}]dec-2-yl ester, (±)-,

Carbamic acid, [1-[[[1-hydroxymethyl)-2-
phenylethyl]amino]carbonyl]-3-(1H-indol-3-yl)-1-
methylpropyl]-, tricyclo[3.3.1.1^{3,7}]dec-2-yl ester
(hydroxymethyl center is S, other center is RS),

12-Oxa-2,5,ß-triazatetradec-10-enoic acid, 3-[2-
(1H-indol-3-yl)ethyl]-3-methyl-4,5,12-trioxo-7-
phenyl-, tricyclo[3.3.1.1^{3,7}]dec-2-yl ester [TRP center
is R/S mixture, other center is R],

L-Phenylalaninamide, N-[[(1,1-dimethylethoxy)-
carbonyl]-α-methyl]-L-tryptophyl]-L-methionyl-L-α-
aspartyl-,

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Glycine, N-[2-methyl-N-[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-D-tryptophyl]-L-phenylalanyl-,

Carbamic acid, [1-[[[1-(hydroxymethyl)-2-phenylethyl]amino]carbonyl]-2-(1H-indol-3-yl)propyl]-,
tricyclo[3.3.1.1^{3,7}]dec-2-yl ester (hydroxymethyl center S, other centers RS),

2,4-Heptadienoic acid, 6-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)-carbonyl]amino]propyl]amino]-7-phenyl-,
[R,R*,S*-(E,E)]]-, and

Glycine, N-[2-methyl-N-[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-D-tryptophyl]-, phenylmethyl ester.

Table I, below, illustrates representative compounds of the invention. The numbers on the left-hand column in Table I correspond to the compound numbers given above. All of the compounds shown in Table I have their stereochemical configurations shown.

In addition to the compounds shown in Table I, the compounds of the present invention include compounds of formula I wherein the indole moiety is a 2-indolyl.

The compounds of the invention include solvates and hydrates and pharmaceutically acceptable salts of the compounds of formula I.

TABLE I
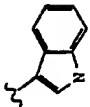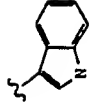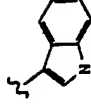
$$R^1-A-E-(CH_2)_m-\overset{\overset{\displaystyle R^2}{|}}{\underset{\underset{\displaystyle Ar^2}{|}}{\overset{|}{C}}}-(CH_2)_p-(X)_q-(CHR^3)_r-(CHR^4)_s-(Y)_t-(CR^{20}R^{12})_u-(CHR^{13})_v-Ar^1$$
$$(CR^5R^6)_n$$

Ex. No.	R¹	A	E	m	R²	p	X	q	R³	r	R⁴	s	y	t	R²⁰	R¹²	R¹³	u	v	Ar¹	R⁵	R⁶	n	Ar²
1	adamantyl	OCONH	Null	O	H	1	NH	1	CH₂OH	1	H	1	Null	O	Null	Null	H	O	1	Ph	H	H	1	indol-3-yl
2	adamantyl	OCONH	Null	O	H	1	NH	1	CH₂OH	1	H	1	Null	O	Null	Null	H	O	1	Ph	H	H	1	indol-2-yl
3	adamantyl	OCONH	Null	O	H	O	NHCO	1	CH₂OH	1	H	1	Null	O	Null	Null	H	O	1	Ph	H	H	1	indol-3-yl

TABLE I

Ex. No.	R1	A	E	m	R2	p	X	q	R3	r	R4	s	y	t	R20	R12	R13	u	v	Ar1	R5	R6	n	Ar2
5		OCONH	Null	O	Me	1	Null	1	H	1	OH	1	Null	O	Null	Null	H	O	1	Ph	H	H	1	
6		OCONH	Null	O	Me	1	NH	1	CH_2OH	1	Null	O	Null	O	Null	Null	H	O	1	Ph	H	H	1	
7		OCONH	Null	O	Me	1	NH	1	CH_2OAc	1	Null	O	Null	O	Null	Null	H	O	1	Ph	H	H	1	
8		OCONH	Null	O	Me	1	NAc	1	CH_2OH	1	Null	O	Null	O	Null	Null	H	O	1	Ph	H	H	1	

TABLE I
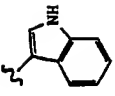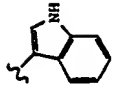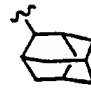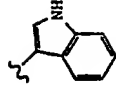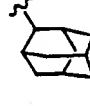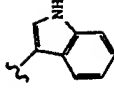
Ex. No.	R1	A	E	m	R2	p	X	q	R3	r	R4	s	y	t	R20	R12	R13	u	v	Ar1	R5	R6	n	Ar2
11	(adamantyl)	OCONH	Null	0	Me	0	COO	1	H	1	Ph	1	NHCO	1	H	-	-	1	1	CO2Me	H	H	1	(indole)
12	(adamantyl)	OCONH	Null	0	Me	0	COO	1	H	1	Ph	1	NHCO	1	H	H	H	1	1	CO2Me	H	H	1	(indole)
19	(adamantyl)	OCONH	Null	0	Me	1	NHCO	1	H	1	H	1	Null	1	Null	O	H	0	1	Ph	H	H	1	(indole)
20	(adamantyl)	OCONH	Null	0	Me	1	NHCO	1	Null	0	Null	0	Null	0	Null	Null	Null	0	0	Ph	H	H	1	(indole)

TABLE I

Ex. No.	R¹	A	E	m	R²	p	X	q	R³	r	R⁴	s	y	t	R²⁰	R¹²	R¹³	u	v	Ar¹	R⁵	R⁶	n	Ar²
21	adamantyl	OCONH	Null	O	Me	1	NHCO	1	H	1	Null	O	Null	O	Null	O	H	O	1	Ph	H	H	1	indolyl
22	adamantyl	OCONH	Null	O	Me	1	NHCO	1	H	1	Null	O	Null	O	Null	Null	H	O	1	Ph	H	H	1	indolyl
23	adamantyl	OCONH	Null	O	Me	O	CONH	1	H	1	H	1	CONH	1	CH_2OH	H	H	1	1	Ph	H	H	1	indolyl
24	adamantyl	CONH	Null	O	Me	O	CONH	1	H	1	H	1	CONH	1	CH_2OH	H	H	1	1	Ph	H	H	1	indolyl

TABLE I

Ex. No.	R¹	A	E	m	R²	p	X	q	R³	r	R⁴	s	y	t	R²⁰	R¹²	R¹³	u	v	Ar¹	R⁵	R⁶	n	Ar²
25	(adamantyl)	OCONH	Null	O	Me	O	CONH	1	H	1	H	1	CONH	1	CONH₂	H	H	1	1	Ph	H	H	1	(indol-3-yl)
26	(adamantyl)	OCONH	Null	O	Me	O	CONH	1	H	1	H	1	CONH	1	CONH₂	H	H	1	1	Ph	H	H	1	(indol-3-yl)
27	(adamantyl)	OCONH	Null	O	Me	O	CONH	1	H	1	H	1	CONH	1	CONH₂	H	H	1	1	Ph	H	H	1	(indol-3-yl)
28	(adamantyl)	OCONH	Null	O	Me	O	CONH	1	H	1	H	1	CONH	1	CONH₂	H	H	1	1	Ph	H	H	1	(indol-3-yl)

TABLE I

Ex. No.	R¹	A	E	m	R²	p	X	q	R³	r	R⁴	s	y	t	R²⁰	R¹²	R¹³	u	v	Ar¹	R⁵	R⁶	n	Ar²
29	adamantyl	OCONH	Null	O	Me	O	NH	1	H	1	H	1	CONH	1	CO_2Me	H	H	1	1	Ph	S	S	1	indol-3-yl
30	adamantyl	OCONH	Null	O	Me	O	CONH	1	H	1	H	1	CONH	1	CO_2O_2	H	H	1	1	Ph	H	H	1	indol-3-yl
31	adamantyl	OCONH	Null	O	Me	O	CONH	1	H	1	H	1	CONH	1	CO_2Bz	H	H	1	1	Ph	H	H	1	indol-3-yl
32	adamantyl	OCONH	Null	O	Me	O	CONH	1	H	1	H	1	CONH	1	CO_2H	H	H	1	1	Ph	H	H	1	indol-3-yl
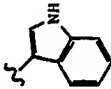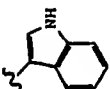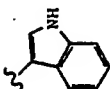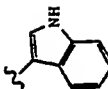
TABLE I

Ex. No.	R¹	A	E	m	R²	p	X	q	R³	r	R⁴	s	y	t	R²⁰	R¹²	R¹³	u	v	Ar¹	R⁵	R⁶	n	Ar²
33	adamantyl	OCONH	Null	O	Me	O	CONH	1	H	1	H	1	CONH	1	CO_2H	H	H	1	1	Ph	H	H	1	indol-3-yl
34	adamantyl	OCONH	Null	O	Me	O	$CONH_2$	1	H	1	H	1	CONH	1	CO_2H	H	H	1	1	Ph	H	H	1	indol-3-yl
35	adamantyl	OCONH	Null	O	Me	O	CONH	1	H	1	H	1	CONH	1	CO_2H	H	H	1	1	Ph	H	H	1	indol-3-yl
36	adamantyl	OCONH	Null	O	Me	O	CONH	1	H	1	Null	O	COO	1	Null	O	H	O	1	Ph	H	H	1	indol-3-yl

TABLE I

Ex. No.	R^1	A	E	m	R^2	p	X	q	R^3	r	R^4	s	y	t	R^{20}	R^{12}	R^{13}	u	v	Ar^1	R^5	R^6	n	Ar^2
37	adamantyl	OCONH	Null	0	$-\overset{O}{\underset{}{C}}-$	1	CON	1	1	1	Null	0	Null	0	Null	Null	H	0	1	Ph	H	H	1	indolyl
39	adamantyl	OCONH	Null	0	Me	0	CONH	1	H	1	Null	0	Null	0	Null	Null	H	0	1	Ph	H	H	2	indolyl
40	adamantyl	O NH C=O	Null	0	Me	0	CONH	1	CO_2OH	1	Null	0	Null	0	Null	Null	H	0	1	Ph	H	H	2	indolyl
41	adamantyl	H N C=O	-	0	Me	0	NH	1	Ph	1	-	-	O NH C=O	1	H	-	-	1	1	CO_2Me	H	H	2	indolyl

TABLE I

Ex. No.	R¹	A	E	m	R²	p	X	q	R³	r	R⁴	s	Y	t	R²⁰	R¹²	R¹³	u	v	Ar¹	R⁵	R⁶	n	Ar²
43	adamantyl	OCONH	Null	0	Me	0	CONH	1	CH₂Ph	1	Null	0	CONH	1	Null	Null	H	0	1	CO₂H	H	H	1	indolyl
44	adamantyl	OCONH	Null	0	H	0	CONH	1	CH₂OH	1	Null	0	Null	0	Null	Null	H	0	1	Ph	Me	H	1	indolyl
45	adamantyl	OCONH	Null	0	Me	0	CONH	1	CH₂Ph	1	Null	0	Null	0	H	-	-	1	1	CH₂–CH₂–CO₂H	H	H	1	indolyl
46	adamantyl	OCONH	Null	0	Me	0	CONH	1	H	1	Null	0	COO	1	Null	Null	H	0	1	Ph	H	H	1	indolyl

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Other examples of compounds of the invention include:

Tricyclo[3.3.1.1^{3,7}]dec-2-ylcarbamic acid, 2-[[2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino]-1-(1H-3-ylmethyl)-1-methyl-2-oxoethyl ester,

N-[2-Hydroxy-1-(hydroxymethyl)-2-phenylethyl]-α-methyl-α-(2-oxo-2-tricyclo[3.3.1.1^{3,7}]dec-2-ylethoxy)-1H-indole-3-propanamide,

N-[2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]-α-(2-hydroxy-2-tricyclo[3.3.1.1^{3,7}]dec-2-ylethoxy)-α-methyl-1H-indole-3-propanamide,

[(Tricyclo[3.3.1.1^{3,7}]dec-2-ylamino)carbonyl]-sulfamic acid, 2-[[2-(hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl ester,

[(Tricyclo[3.3.1.1^{3,7}]dec-2-ylamino)sulfonyl]-carbamic acid, 2-[[2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl ester,

[[2-[[2-Hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethoxy]sulfonyl]carbamic acid, tricyclo[3.3.1.1^{3,7}]-dec-2-yl ester,

N-[2-Hydroxy-1-(hydroxymethyl)-2-phenylethyl]-methyl-[[2-oxo-2-(tricyclo[3.3.1.1^{3,7}]dec-2-ylamino)-ethyl]amino]-1H-indole-3-propanamide,

N-[2-Hydroxy-1-(hydroxymethyl)-2-phenylethyl]-α-methyl-α-[[(tricyclo[3.3.1.1^{3,7}]dec-2-ylamino)acetyl]-amino]-1H-indole-3-propanamide,

N-[2-Hydroxy-1-(hydroxymethyl)-2-phenylethyl]-α-methyl-α-[(2-oxo-2-tricyclo[3.3.1.1^{3,7}]dec-2-ylethyl)amino]-1H-indole-3-propanamide,

N-[2-Hydroxy-1-(hydroxymethyl)-2-phenylethyl]-α-[(2-hydroxy-2-tricyclo[3.3.1.1^{3,7}]dec-2-ylethyl)amino]-α-methyl-1H-indole-3-propanamide,

-33-

N-[2-Hydroxy-1-(hydroxymethyl)-2-phenylethyl]-α-
methyl-α-[[[[(tricyclo[3.3.1.1^{3,7}]dec-2-ylamino)-
carbonyl]amino]sulfonyl]amino]-1H-indole-3-
propanamide,

5   N-[2-Hydroxy-1-(hydroxymethyl)-2-phenylethyl]-α-
methyl-α-[[[[(tricyclo[3.3.1.1^{3,7}]dec-2-ylamino]-
sulfonyl]amino]carbonyl]amino]-1H-indole-3-
propanamide,

         [[[2-[[2-Hydroxy-1-(hydroxymethyl)-2-phenyl-
10   ethyl]amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-
oxoethyl]amino]sulfonyl]carbamic acid,
tricyclo[3.3.1.1^{3,7}]dec-2-yl ester,

         [[[2-[[2-Hydroxy-1-(hydroxymethyl)-2-
phenylethyl]amino]-1-(1H-indol-3-ylmethyl]-1-methyl-2-
15   oxoethyl]amino]carbonyl]sulfamic acid,
tricyclo[3.3.1.1^{3,7}]dec-2-yl ester,

         N-[2-Hydroxy-1-(hydroxymethyl)-2-phenylethyl]-α-
methyl-α-[[(tricyclo[3.3.1.1^{3,7}]dec-2-ylamino)-
sulfonyl]amino]-1H-indole-3-propanamide,

20   N-[2-Hydroxy-1-(hydroxymethyl)-2-phenylethyl]-2-
(1H-indol-3-ylmethyl)-2-methyl-N'-(tricyclo-
[3.3.1.1^{3,7}]dec-2-ylmethyl)propanediamide,

         N-[2-Hydroxy-1-(hydroxymethyl)-2-phenylethyl]-2-
(1H-indol-3-ylmethyl)-2-methyl]N'-tricyclo[3.3.1.1^{3,7}]-
25   dec-2-ylpropanediamide,

         N-[2-Hydroxy-1-(hydroxymethyl)-2-phenylethyl]-α-
[[imino(tricyclo[3.3.1.1^{3,7}]dec-2-ylamino)methyl]-
amino]-α-methyl-1H-indole-3-propanamide,

         α-[[(Cyanoimino)(tricyclo[3.3.1.1^{3,7}]dec-2-
30   ylamino)methyl]amino]-N-[2-hydroxy-1-(hydroxymethyl)-
2-phenylethyl]-α-methyl-1H-indole-3-propanamide,

         N-[2-Hydroxy-1-(hydroxymethyl)-2-phenylethyl]-α-
methyl-α-[[(nitroimino)(tricyclo[3.3.1.1^{3,7}]dec-2-
ylamino)methyl]amino]-1H-indole-3-propanamide,

-34-

   [2-[[2-Hydroxy-1-(hydroxymethyl)-2-
phenylethyl]amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-
oxoethyl]phosphoramidic acid, phenyl
tricyclo[3.3.1.1^{3,7}]dec-2-yl ester,

5   N-[2-[[2-Hydroxy-1-(hydroxymethyl)-2-
phenylethyl]amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-
oxoethyl]-N-tricyclo[3.3.1.1^{3,7}]dec-2-
ylphosphorodiamidic acid phenyl ester,

   Tricyclo[3.3.1.1^{3,7}]dec-2-ylphosphoramidic acid,
10   2-[[2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]amino]-
1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl phenyl
ester, and

   Phosphoric acid, 2-[[2-hydroxy-1-(hydroxy-
methyl)-2-phenylethyl]amino]-1-(1H-indol-3-ylmethyl)-
15   1-methyl-2-oxoethyl phenyl tricyclo[3.3.1.1^{3,7}]dec-2-yl
ester.

   The compounds of the present invention can have
multiple chiral centers including those designated in
the above formula I by the symbol †, depending on
20   their structures. For example, when R^3 taken with R^4
and R^{12} taken with R^{13} form double bonds to their
carbon atoms, they are no longer chiral. In addition,
centers of asymmetry may exist on the other
substituents. In particular, the compounds of the
25   present invention may exist as diastereomers, mixtures
of diastereomers, or as the mixed or the individual
optical enantiomers. The present invention
contemplates all such forms of the compounds. The
mixtures of diastereomers are typically obtained as a
30   result of the reactions described more fully below.
Individual diastereomers may be separated from
mixtures of the diastereomers by conventional
techniques such as column chromatography or repetitive
recrystallizations. Individual enantiomers may be
35   separated by convention method well known in the art

-35-

such as conversion to a salt with an optically active
compound, followed by separation by chromatography or
recrystallization and reconversion to the nonsalt
form.

5   The compounds of the present invention can be
formed by coupling individual substituted ∝-amino
acids by methods well known in the art. (See, for
example, standard synthetic methods discussed in the
multi-volume treatise "The Peptides, Analysis,
10   Synthesis, Biology," by Gross and Meienhofer, Academic
Press, New York.) The individual substituted alpha
amino acid starting materials are generally known or,
if not known, may be synthesized and, if desired,
resolved by methods within the skill of the art.
15   (Synthesis of racemic [DL]-∝-methyl tryptophan methyl
ester - see Braña, M. F., et al, <u>J. Heterocyclic
Chem.</u>, 1980, 17:829.)

        A key intermediate in the preparation of
compounds of formula I is a compound of formula
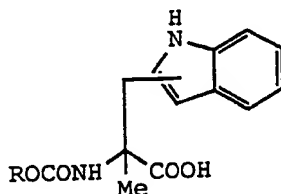
20   II

wherein R is selected from R^1, 9-fluorenylmethyl, Bz
and other suitable N-blocking groups. These are
useful as intermediates in the preparation of
compounds of formula I. The compounds wherein R is 1-
25   adamantyl, 2-adamantyl, 4-protoadamantyl, exo-bornyl,
endo-bornyl, exo-norbornyl, endo-norbornyl, 2-
methylcyclohexyl, 2-chlorocyclohexyl, or camphoryl are
novel and are preferred.

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The disclosure of U.S. 4,757,151 is hereby incorporated by reference. It describes the 9-fluorenylmethyl blocking group.

Compounds of formula II are prepared by reacting

5   ROH   III

wherein R is as defined above, with phosgene or a phosgene substitute to produce a corresponding compound of formula

                          ROCOCl   IV

10   and then reacting a compound of formula IV with α-methyltryptophan to produce the desired compound of formula II above.

Alternatively, a compound of formula IV can be reacted with an α-methyltryptophan methyl ester to
15   produce
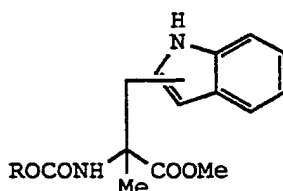
V

which can be converted to a compound of formula II by known means such as hydrolysis with aqueous lithium hydroxide.
20   The schemes below illustrate procedures for preparing intermediates useful in producing final products of formula I.

-37-

   Scheme I below illustrates preparative steps in
the process of making compounds of the instant
invention. Treatment of 2-adamantyloxycarbonyl-
tryptophan 1 with N-methylmorpholine followed by
5   isobutylchloroformate gave an intermediary mixed
anhydride, this when mixed with N,O-dimethylhydro-
acylamine hydrochloride gave the hydroxamate 2 which
yielded the aldehyde 3 on reduction with $LiAlH_4$.
Reductive amination of 3 with S-phenylalaninol and
10   $NaCNBH_3$ gave the amino methylene 4 (Example 1).
Example 2 (compound 5) was prepared in an exactly
analogous manner. The intermediate mixed anhydride
described above was treated with Me_3SiN_3 to make the
acid azide which then reacted with p-nitrobenzyl
15   alcohol in the presence of DABCO to give the bis
urethane 6. Hydrogenation using Pearlman's catalyst
to the monourethane, and treatment of the amine with
the HOBT ester of 2-(acetoxymethyl)-3-phenylpropionic
acid gave the compound 7, Example 3 after
20   saponification of the ester with LiOH in aqueous THF.
Example 4, compound 10 was prepared in three steps
from 1. Here the mixed anhydride of 1 was treated
with diazomethane to give the diazoketone 8. Reaction
with HCl to the chloro ketone followed by reaction
25   with sodium diethylbenzyl malonate gave a diester
which, upon saponification, decarboxylated to the acid
10, Example 4.

-38-

SCHEME 1

7 Example 3

4 Example 1 = R
5 Example 2 = S

10 Example 4
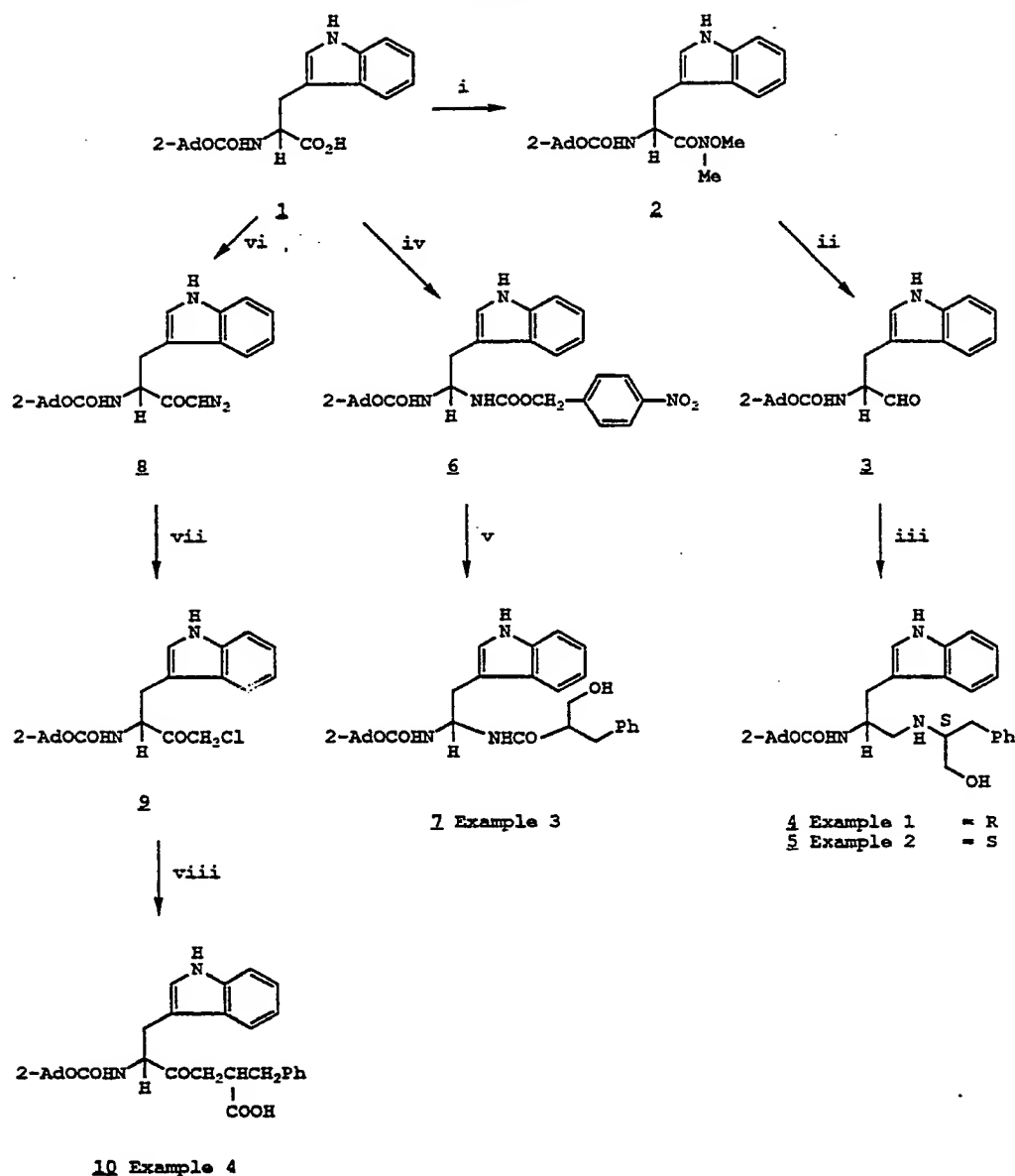
KEY   i) isobutylchloroformate, N-methyl morpholine,
CH$_3$ONH(CH$_3$)·HCl; ii) LiAlH$_4$; iii) S-phenylalaninol, NaCNBH$_3$;
iv) isobutylchloroformate, N-methylmorpholine, Me$_3$SiN$_3$ then
40°C then <u>para</u>-NO$_2$-C$_6$H$_4$CH$_2$OH, DABCO;
2,4-diazabicyclo[2.2.2]octane (DABCO); v) Pd(OH)$_2$ H$_2$, then
RS-HO$_2$CCH(CH$_2$Ph)CH$_2$OAc; then LiOH, THF;
vi) isobutylchloroformate, N-methylmorpholine, CH$_2$N$_2$;
vii) HCl-dioxane; viii) NaI, NaOME, then
sodiodiethylbenzylmalonate, then NaOH, then HCl, then heat.

Scheme 2

    Example 5, compound 12 was prepared by reduction of the amide in 11 using $LiBH_4$ and Me_3SiCl. Similarly, Example 6, compound 14 was prepared from 13. 14 was treated with acetylchloride to give Example 7, in the presence of base. The major product was compound 15a, which was hydrolyzed to Example 8, compound 16, on treatment with lithium hydroxide. The thiazoline 17, Example 9, was prepared by heating 13 with Lawesson's reagent.

-40-

SCHEME 2

29   30 Example 9

11   12 Example 5

13   14 Example 6

17 Example 16

15 Example 7   R¹ = H, R² = Ac
16 Example 8   R¹ = Ac, R² = H
15c   R¹ = Ac, R² = Ac
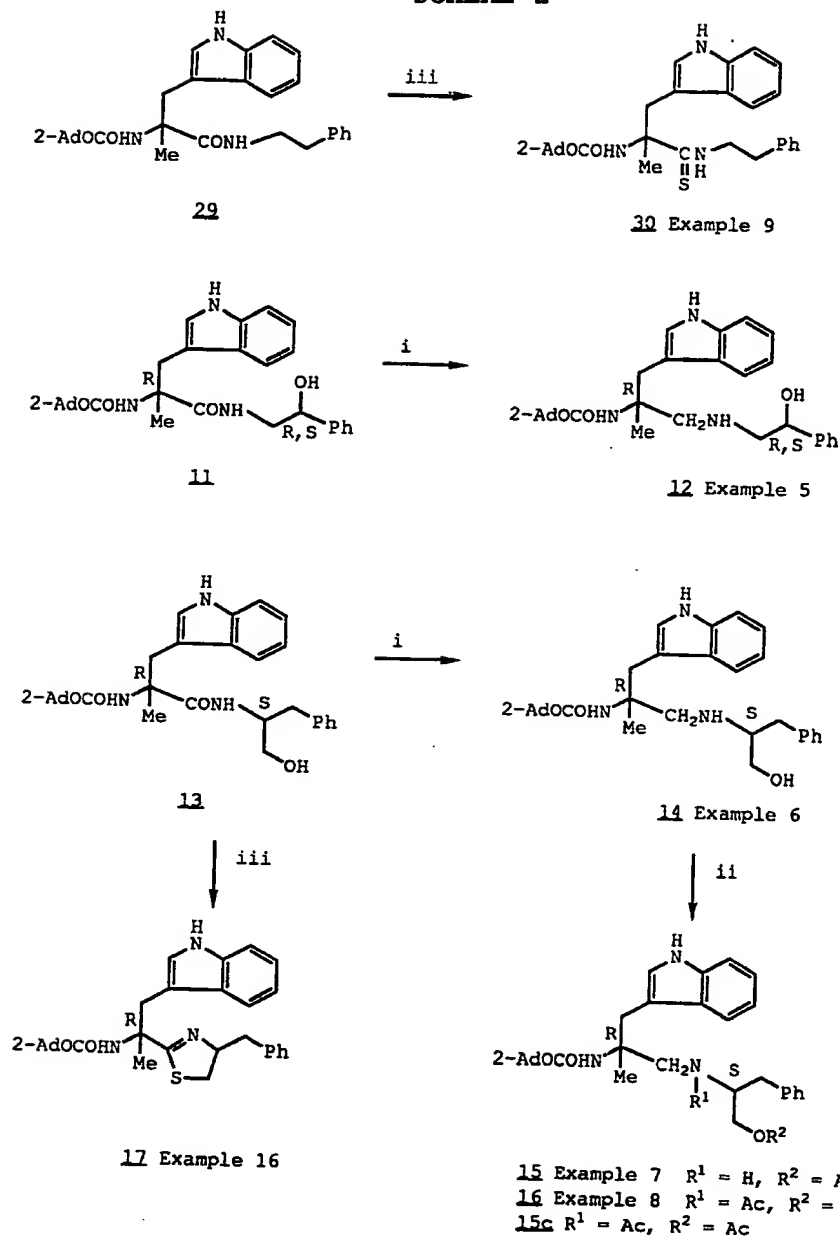
KEY i) LiBH₄, Me₃SiCl; ii) CH₃COCl (Example 7); or CH₃COCl, Et₃N
then LiOH (Example 8); iii) Lawesson's Reagent.

-41-

   Scheme 3 shows the synthesis of examples of ester
isosteres. Monomethylfumarate was condensed with
R-phenylglycinol via its HOBT ester to give 18.
Further condensation of this with R- or S
5   2-Adoc-α-MeTrpOH in the presence of
N,N'-carbonyldiimidazole gave Examples 10
(compound 19) and 11 (compound 20), respectively. In
an exactly analogous way Example 12 (compound 22) was
made except using monomethyl succinate.

-42-

SCHEME 3

19 Example 10   = R-configuration
20 Example 11   = S-configuration

22 Example 12
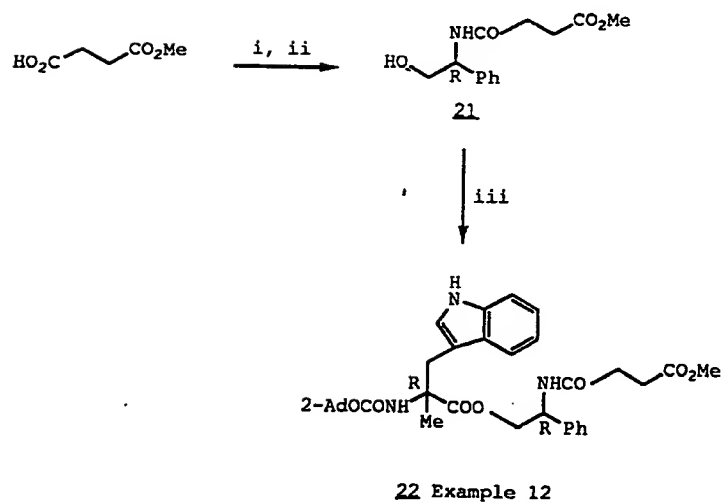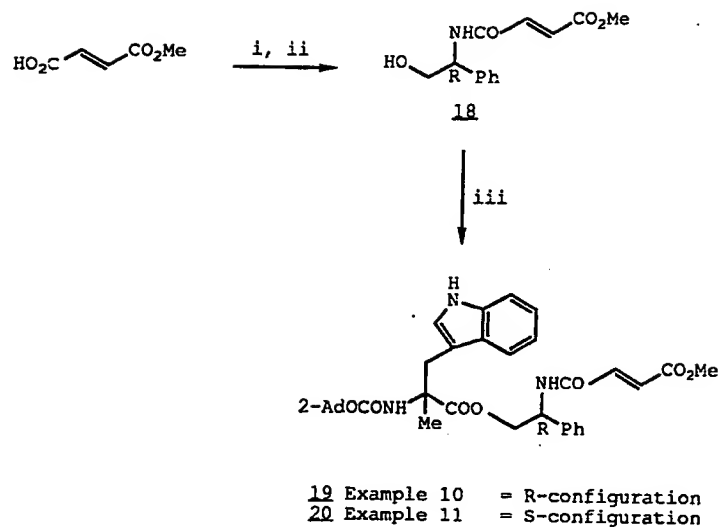
KEY   i) HOBT, DCCI; ii) R-phenylalaninol; iii) R- or S-
       2-Adoc-αMeTrp-OH (Compound 23).

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Scheme 4

Reduction of 23a to the primary alcohol 24 with
$LiAlH_4$ followed by treatment with phenyl acetic acid
and N,N'-carbonyldiimidazole gave the ester isostere
25, Example 13. Oxidation of 24 to the aldehyde 26
provided a very versatile intermediate. This aldehyde
26 was treated with Wittig reagents to give 27
(Example 14) and 29. Compound 29 was modified further
to 30, Example 16 by hydrolysis of the ester and
subsequent condensation with aniline. Treatment of
aldehyde 26 with the Grignard reagent 3-phenylpropyl
magnesium bromide afforded the secondary alcohol 28
(Example 15).

-44-

SCHEME 4

23

24

26

25 Example 13

27 Example 14

28 Example 15
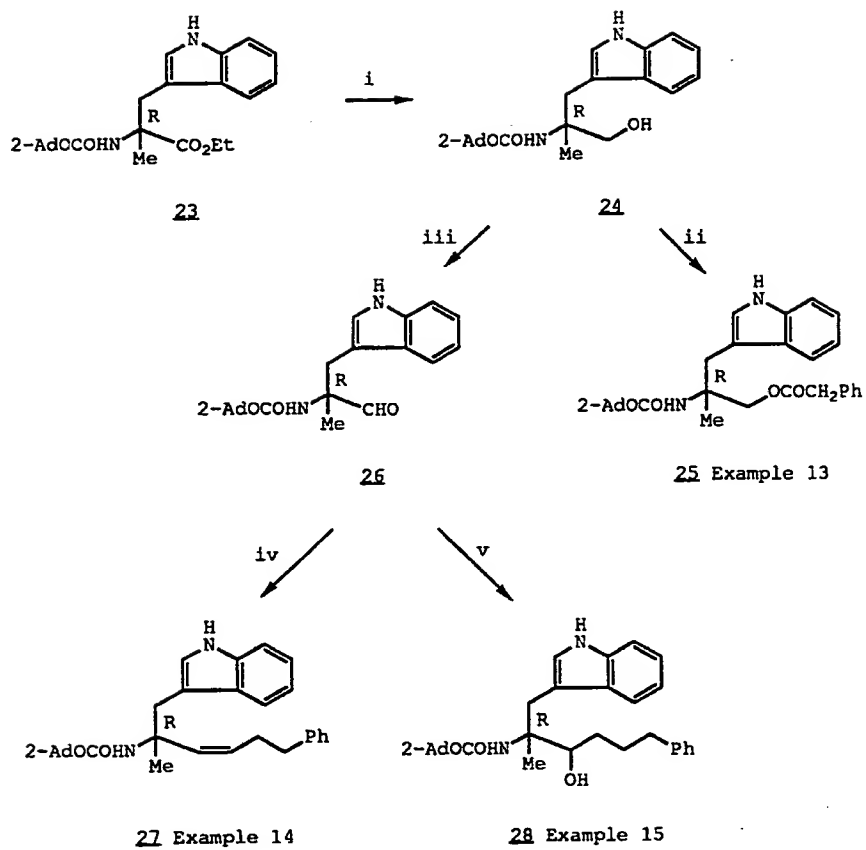
KEY   i) LiAlH₄; ii) PhCH₂CO₂H; carbonyldiimidazole;
iii) Tetrapropylammonium perruthenate; iv) PhCH₂CH₂P⁺Ph₃Br⁻,
NaH; v) PhCH₂CH₂CH₂MgBr.

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Scheme 5 shows the synthetic routes to some examples of homologated α-methyltryptophans, and their reverse amide isosteres. The mixed anhydride of 23b prepared by using isobutylchloroformate and

5   N-methylmorpholine was treated with diazomethane to give the diazoketone 31, this as a solution in benzyl alcohol was treated with silver benzoate and Et₃N to yield the homologated benzyl ester 32. Hydrogenation afforded the acid 33 which was condensed in the usual

10   way via the pentafluorophenyl ester with S-phenyl alaninol to give 34 (Example 18).

The amide of 23b, 35 was prepared by bubbling ammonia gas through a solution of the pentafluorophenyl ester. This amide was reduced to

15   the amine 36 with Me₃SiCl/LiBH₄ in THF. This amine was subsequently reacted with phenyl acyl chlorides to give Examples 19-22 inclusive.

SCHEME 5

37a	M	ExN°
37a	0	20
b	1	22
c	2	21
d	3	19
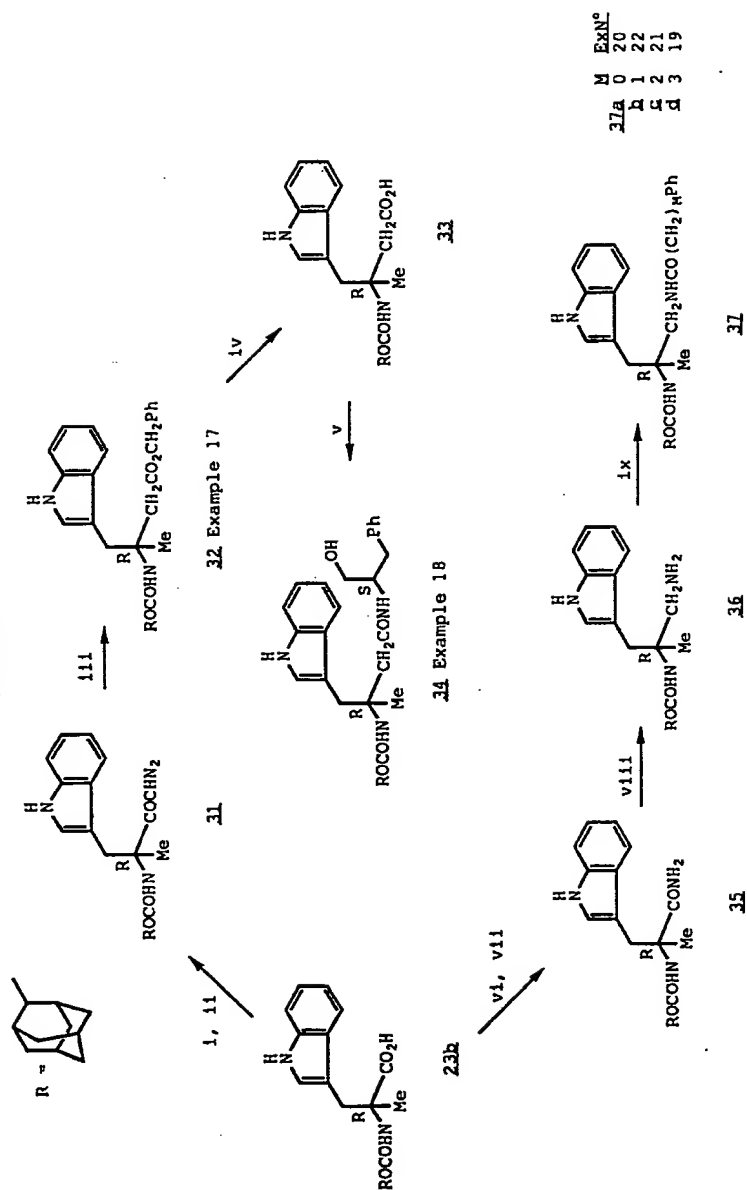
KEY <u>Reagents</u>: i) isobutylchloroformate, NMM, THF; ii) CH$_2$N$_2$, EtOAc; iii) Ag$^+$ $^-$OCOPh, Et$_3$N, PhCH$_2$OH; iv) H$_2$/Pd/C; v) PFP, DCC, H$_2$NCH(CH$_2$OH)CH$_2$Ph, EtOAc; vi) PFP, DCC, EtOAc; vii) NH$_3$(g), THF; viii) TMS-Cl, LiBH$_4$, THF; ix) Ph(CH$_2$)$_n$COCl, pyridine, EtOAc.

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Scheme 6 illustrates the synthesis of
α-methyltryptophyl-ß-alanine derivatives. The
2-adamantyl oxycarbonyl α-methyltryptophan 23b (R
isomer) or 38 (S isomer) is condensed with ß-alanine
ester in the usual manner. This ester can then be
hydrolyzed using standard methods (e.g., aqueous LiOH,
etc) to afford the carboxylic acid 41 or 42. Either
of these two isomers may be condensed with an
appropriate amine to give Examples 23 and 24 (using
S-phenyl alaninol), Examples 25-28 inclusive (using R
and S phenyl alaninamide) and Examples 29-31 inclusive
(using phenylalanine ester. Examples 29-31 and
compound 52 may then be hydrolyzed using known methods
to afford the products Examples 32-35 inclusive.

-48-

SCHEME 6

	•	Δ	ExN°
43	R	S	23
44	S	S	24

	•	Δ	ExN°
45	R	R	25
46	R	S	26
47	S	S	27
48	S	R	28

	•	Δ	ExN°
49	R	R	29
50	R	S	30
51	S	S	31
52	S	R	—

	•	Δ	ExN°
53	R	R	32
54	R	S	33
55	S	S	34
56	S	R	35
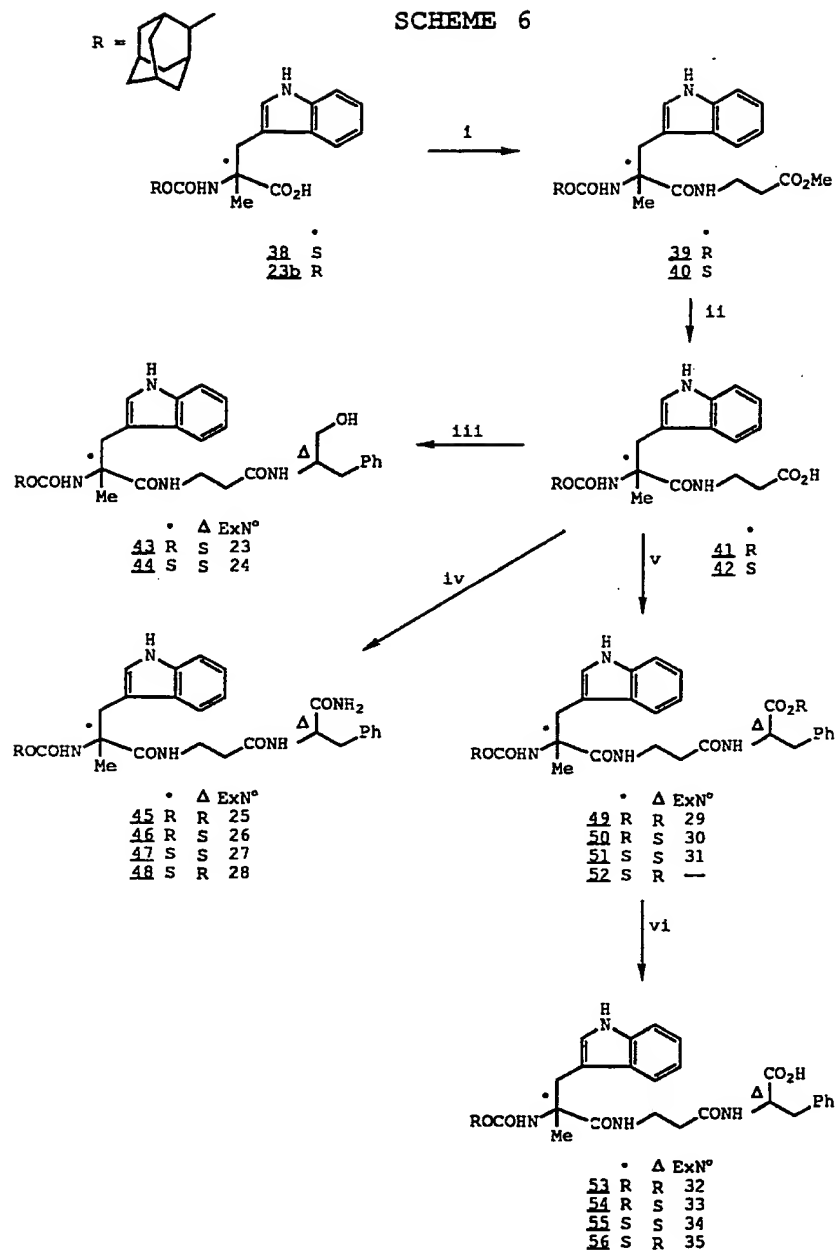
KEY   Reagents: i) PFP, DCC, ß-Alanine Me ester, EtOAc;
ii) LiOH, aq dioxan; iii) DCC, (S)-(-)-2-amino-3-phenyl-1-
propanol EtOAc; iv) PFP, DCC, (R)-phenylalaninamide, EtOAc;
v) PFP, DCC, (S)-phenylalanine benzyl ester, EtOAc or PFP,
DCC, (R)-phenylalanine methyl ester, EtOAc; vi) H₂, Pd/C,
EtOH.

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Scheme 7 describes synthetic steps towards
derivatives of α-methyl tryptophyl glycine. As an
illustration, 2-Adoc-α-methyltryptophan 23b may be
easily condensed with glycine benzyl ester via the
5   pentafluorophenyl ester of 23b. Hydrogenation of this
ester using 10% palladium on carbon in an ethanol
solution affords the carboxylic acid 58 in high yield.
Treatment of this acid with N,N'dicyclohexyl-
carbodiimide and pentafluorophenol gives the active
10   ester which undergoes reaction with phenylalaninol
readily to give the product compound 59, Example 37.

-50-

SCHEME 7

23b

57 Example 36

59 Example 37

58
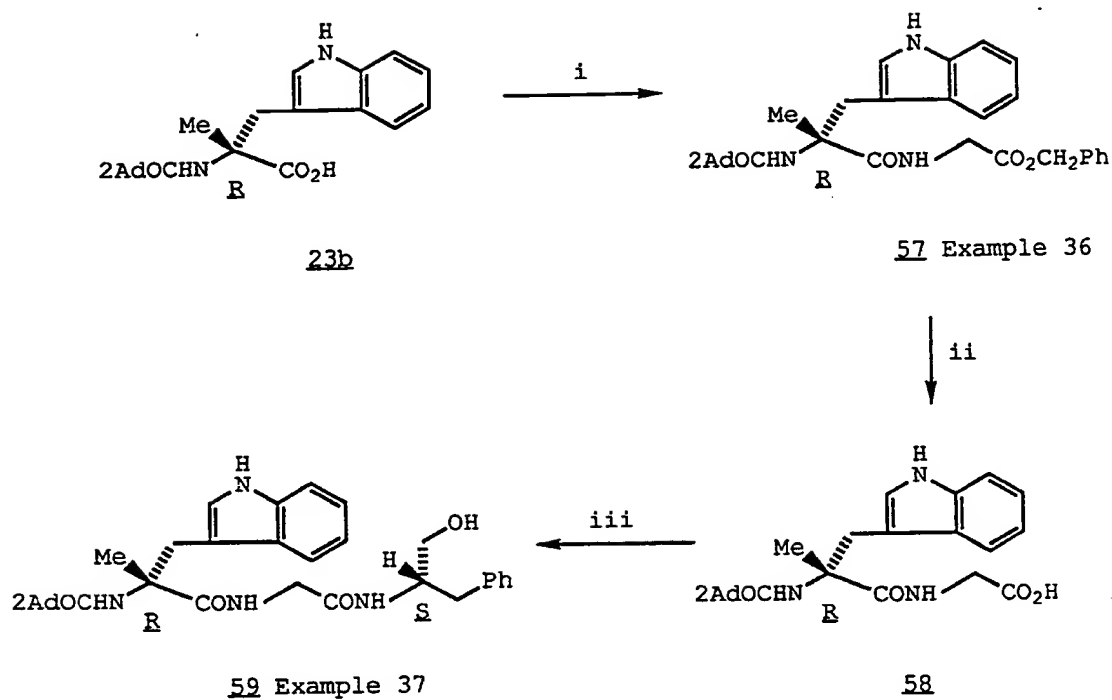
KEY   Reagents: i) PFP, DCC, glycine benzyl ester hydrochloride,
       Et₃N, EtOAc; ii) H₂ Pd/C, EtOH; iii) PFP, DCC,
       s-phenylalaninol, EtOAc.

Scheme 8 describes synthetic steps towards
derivatives of α-methyltryptophyl-γ-aminobutyric
acids. As an illustration, the carboxylic acid 23b
may be condensed with γ-aminobutyric acid methyl ester
to give 60, hydrolysis of this with LiOH affords acid
61. The product 62, Example 39 is produced when 61 is
condensed with phenylalaninol via an active
pentafluorophenyl ester.

-52-

SCHEME 8

-52-
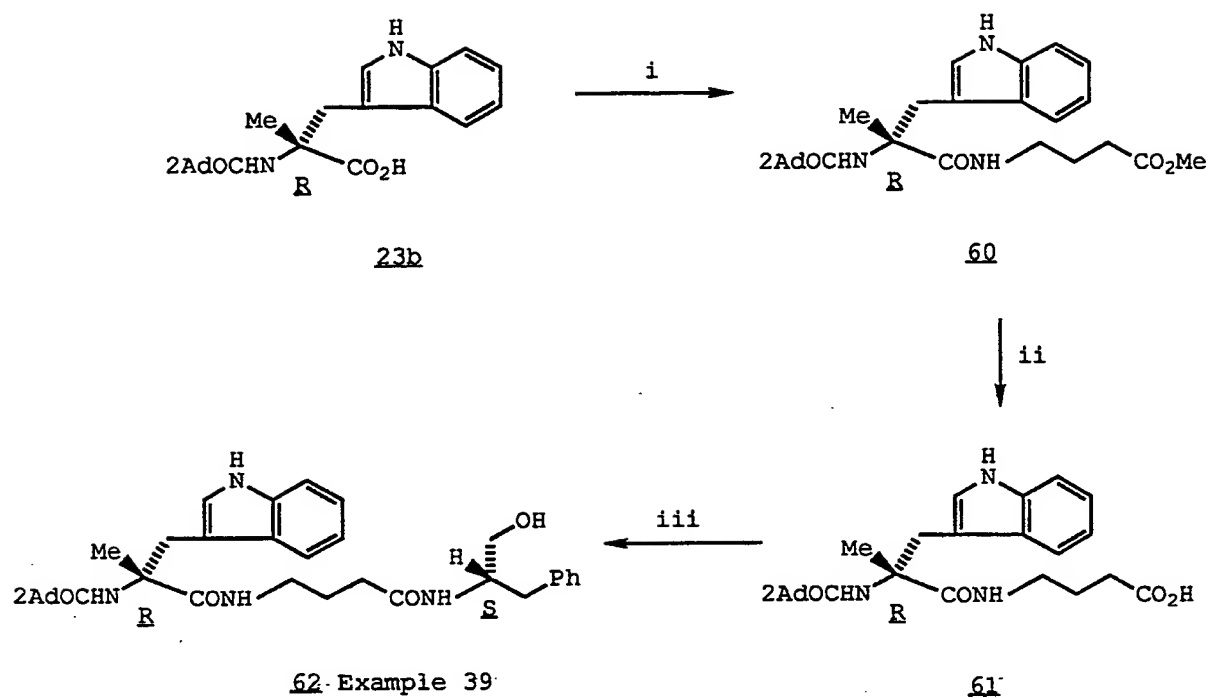
SCHEME 8

KEY   Reagents: i) PFP, DCC, gamma-aminobutyric acid methylester
hydrochloride, Et_3N, EtOAc; ii) LiOH, aq 1,4-dioxan;
iii) PFP, DCC, s-phenylalaninol, EtOAc.

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Scheme 9 outlines the synthesis of α-substituted
tryptophanylphenethylamides and their intramolecular
cyclizations to compound 68, Example 40. The
isonitrile 63 (prepared by the method described in
Synthesis 465, 1990) in ethanol at -5°C was treated
with ethanolic HCl to give the amine 64. This
underwent coupling with 2-adamantylchloroformate to
the urethane 65. Hydrogenation of 65 using 10%
palladium on charcoal at 45 psi yielded the mono acid
mono ester 66 which was condensed in the usual way to
2-phenethylamine giving 67. The product was formed by
treatment of 67 with LiOH which abstracts the amide NH
proton and cyclizes onto the ester group, liberating
methoxide.

-54-

SCHEME 9
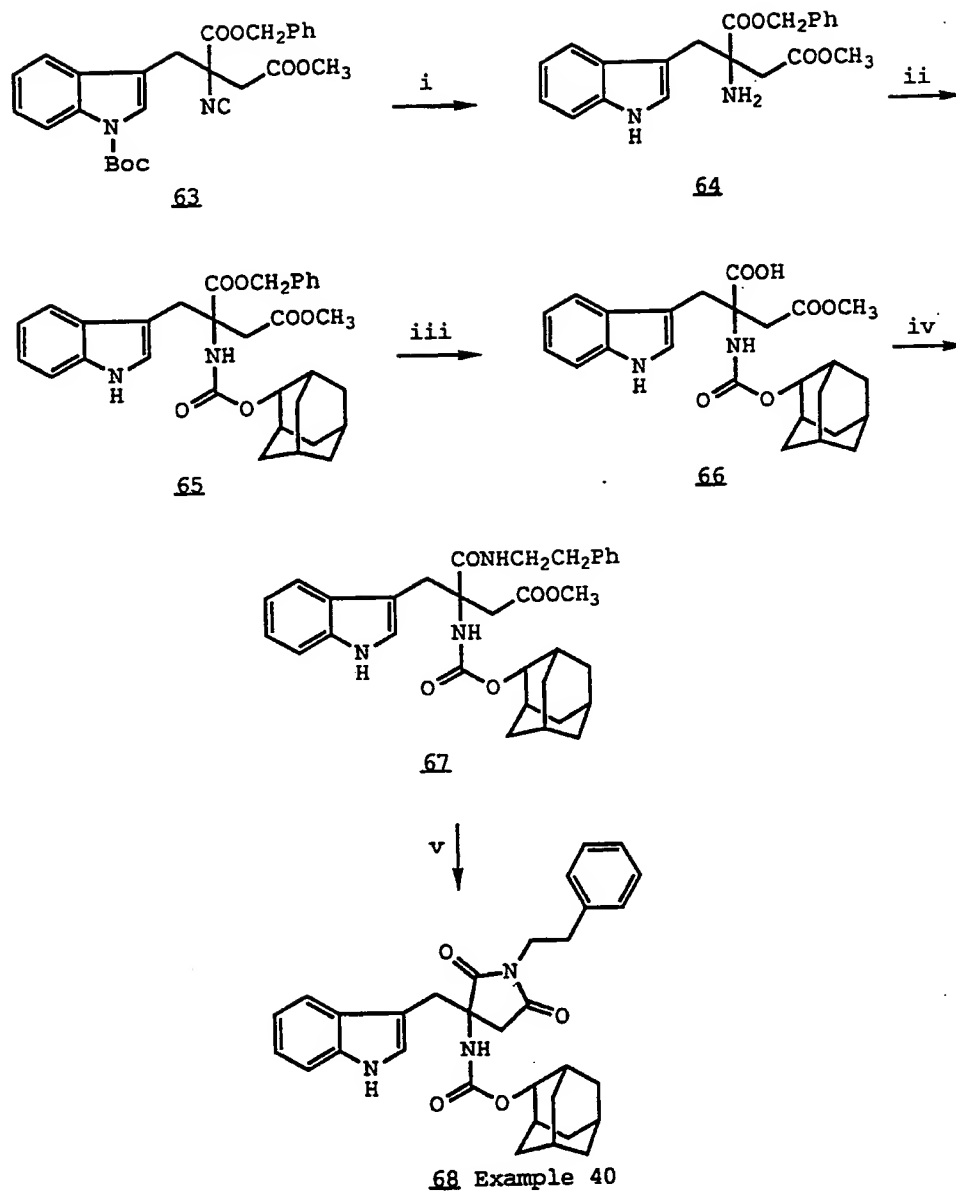
KEY   Reagents: i) EtOH·HCl, 67%; ii) 2-adamantyl-OCOCl, Et₃N,
      EtOAc, 58%; iii) Pd/H₂, EtOH, 88%; iv) H₂NCH₂CH₂Ph, PFP,
      DCC, DMAP, EtOAc, 73%; v) LiOH(0.01M), 0°C, THF/H₂O, 79%.

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Scheme 10 outlines the synthetic steps towards
ß-substituted tryptophan derivatives. Isopropylamine,
when added to acetaldehyde and treated with KOH, gives
69 which reacts with indole in glacial acetic acid
5   over 5 days to produce 70. The isopropylamino
ethylidene 70 then reacts with 71 in the presence of
NaOMe in hot toluene, yielding 72. Saponification and
decarboxylation affords 74 as a mixture of separable
diastereoisomers.
10   The amide 74 is dissolved in 4N sulphuric acid at
reflux, then cooled to ambient temperature, and
treated with 0.4N barium hydroxide until a pH of 8 is
obtained, yielding the free amine 75 which reacts with
2-adamantyl chloroformate 76, yielding the urethane
15   77. This is then condensed with phenyl alaninol in
the normal manner to give the product 78, Example 89.

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SCHEME 10
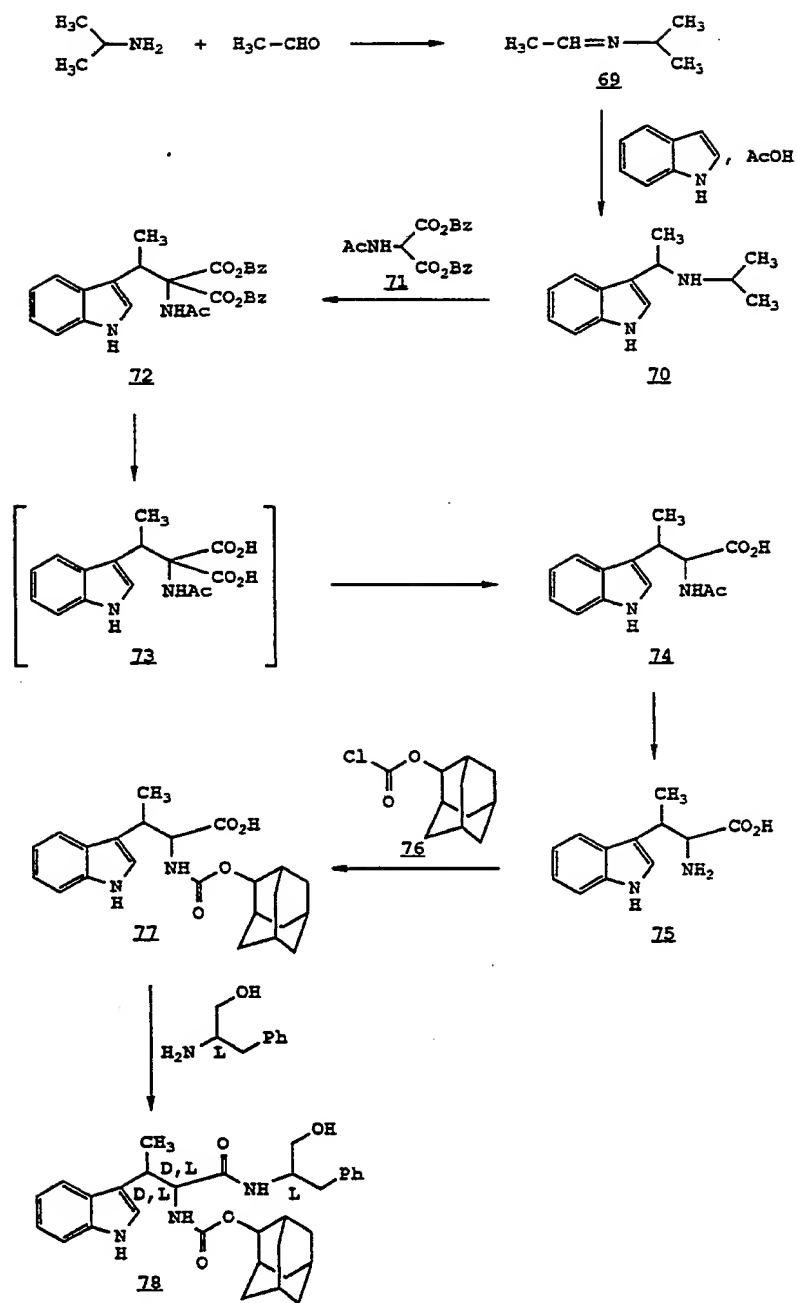
Example **89**

-57-

GENERAL PROCESS FOR REACTION SCHEMES

Scheme 15a:

   Cyano acetic esters or substituted derivatives $\underline{1}$
are alkylated with gramine and a base, e.g., NaOH in
5   toluene, to compounds $\underline{2}$ in analogy to known methods.
Compounds $\underline{2}$ are hydrogenated catalytically with Raney
nickel alloy to the amino esters $\underline{3}$, which are reacted
with chloro- or fluoroformates to the carbamic acid
esters $\underline{4}$. The esters $\underline{4}$ are hydrolyzed to the acids $\underline{5}$,
10   which are converted to activated esters, e.g., with
pentafluorophenol and dicyclohexylcarbodiimide to the
pentafluorophenyl esters. The activated esters are
reacted with an appropriate amine to an amide of
formula 6. Further conversions at the amide part of
15   the molecules are done in analogy to known methods.

Compounds of general formula 15a

$$R^1 - O - CO - NH - CH_2 - \overset{\overset{\displaystyle R^2}{|}}{\underset{\underset{\displaystyle CH_2}{|}}{C}} - CO - NH - (CHR^3)_c - CHR^4 - Ar \qquad \text{Ia}$$
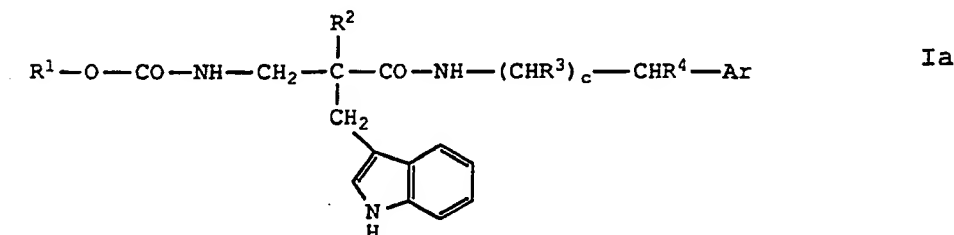
where R^1 = 1-adamantyl, 2-adamantyl,
(1S)-2-endo-bornyl
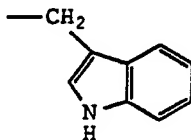
20   R^2 = H or Me   , c = 0 or 1

       R^3 = H, $-CH_2OH$, $-CH_2O-CO-(CH_2)_2CO_2H$

-58-

R^4 = H, $-NH-CO_2-t-Bu$,

$-NH-CO-CH_2-CH_2-CO_2Bz$, $-NH-CO-CH_2-CH_2-CO_2H$

$-NH-CO-CH=CH-CO_2Me$, $-NH-CO-CH=CH-CO_2H$

t   t
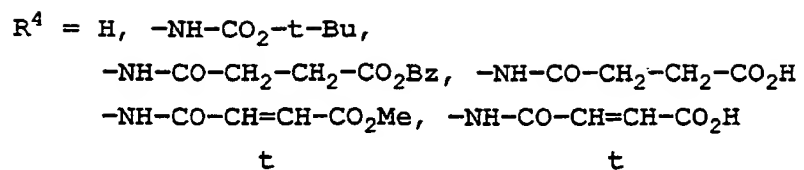
5   are prepared according to <u>Synthetic Scheme 15a</u>:

-59-

SYNTHETIC SCHEME 15a
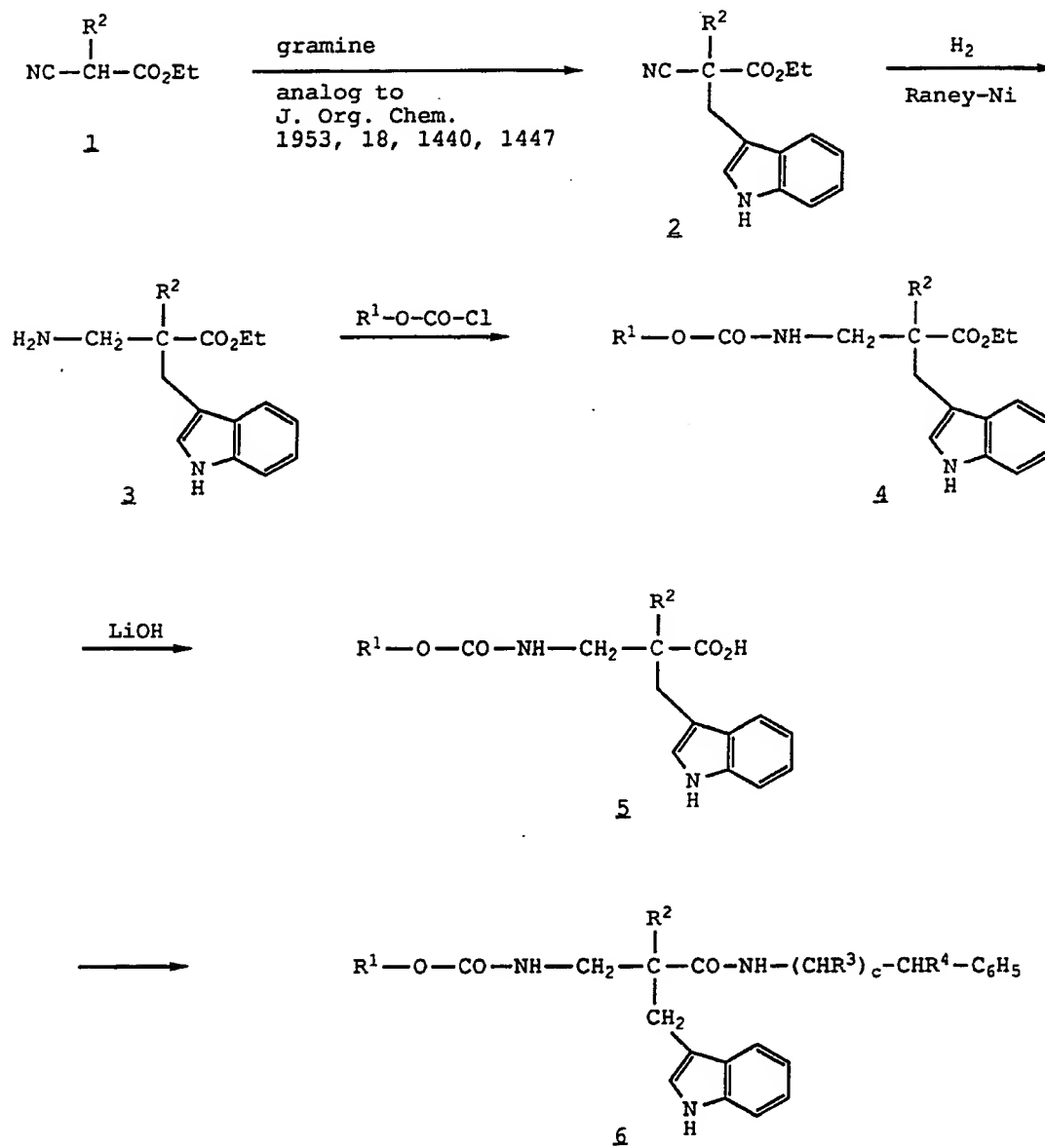
-60-

Scheme 15b:

Compounds of general formula Ia, where R^2, R^3, and R^4 are H are also prepared according to Synthetic Scheme 15b. Cyano acetic esters 7 are reacted with appropriate amines to the cyano acetamides 8, which are condensed with indole-3-carboxaldehyde and catalytic amounts of piperidine to compounds 9 in analogy to known methods, and thereafter hydrogenated catalytically with Raney nickel alloy to the 3-indolylmethyl substituted ß-aminopropionamides 10. Reaction with chloro- or fluoroformates yields the carbamic acid ester derivatives 11.

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SYNTHETIC SCHEME 15b

$NC-CH_2-CO_2Et$ $\xrightarrow{C_6H_5-CH_2(CH_2)_c-NH_2}$ $NC-CH_2-CO-NH-(CH_2)_c-CH_2-C_6H_5$

7

8

analog to JACS *72*, 2982 (1950)

$\xrightarrow[\substack{\text{analog to} \\ \text{J. Org. Chem.} \\ \underline{1953}, \underline{24}, 1165}]{\substack{\text{indole-3-} \\ \text{carboxaldehyde}}}$

$NC-\underset{\underset{\displaystyle CH}{\overset{\|}{C}}}{}-CO-NH-(CH_2)_c-CH_2-C_6H_5$

$\xrightarrow[\text{Raney-Ni}]{H_2}$

9

$H_2N-CH_2-\underset{\underset{\displaystyle CH_2}{|}}{CH}-CO-NH-(CH_2)_c-CH_2-C_6H_5$

10

$R^1-O-CO-Cl$

$R^1-O-CO-NH-CH_2-\underset{\underset{\displaystyle CH_2}{|}}{CH}-CO-NH-(CH_2)_c-CH_2-C_6H_5$

11
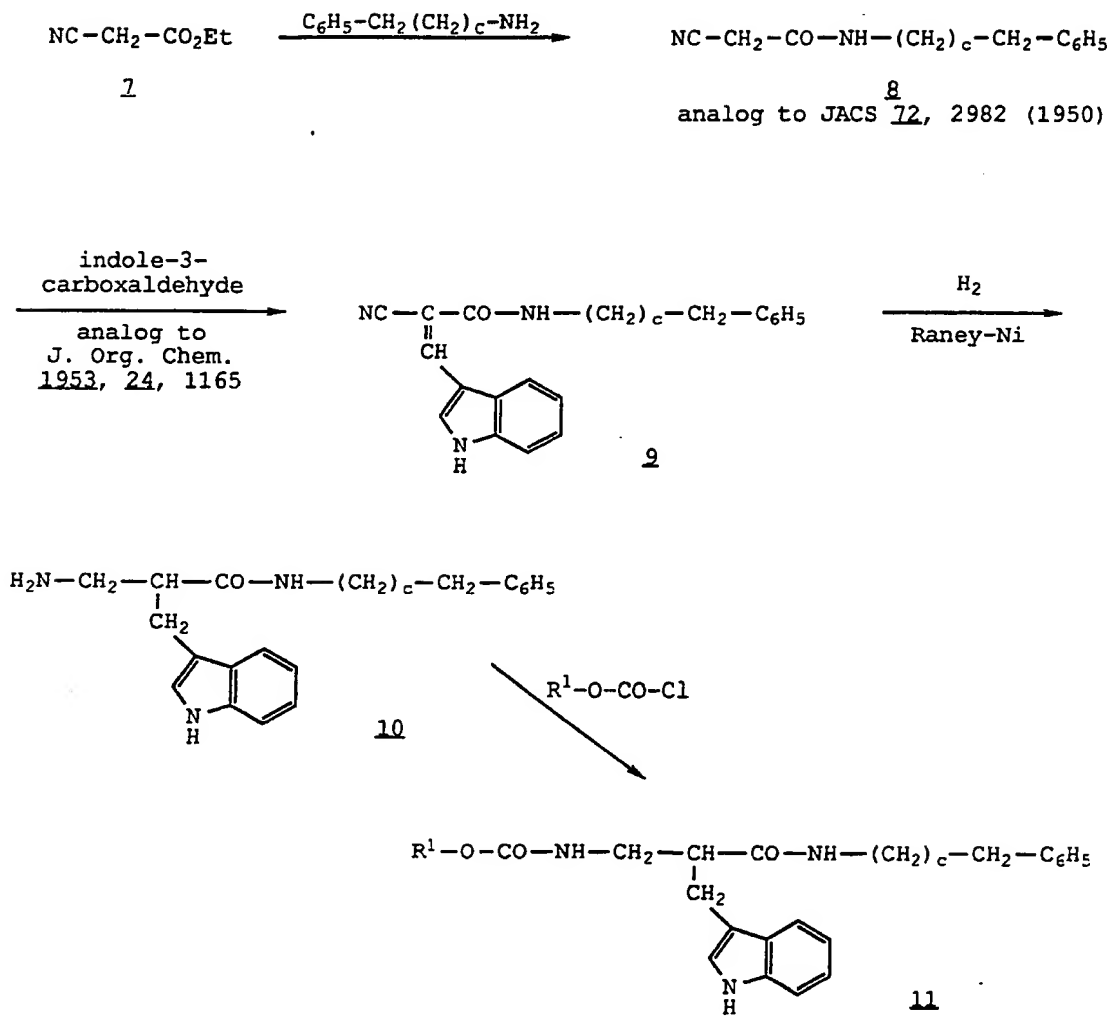
-62-

Scheme 15c:

Compounds of general formula Ia,
where R^2 = H or $-CH_2$
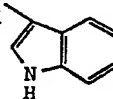
and R^3 and R^4 are H

5   are also prepared according to Synthetic Scheme 15c.
Cyano acetamides 8 are alkylated with gramine and a
base, e.g., NaOH in toluene, to compounds 12 and 13,
which are hydrogenated catalytically with Raney nickel
alloy to the mono- or bis-(3-indolylmethyl)

10   substituted ß-aminopropionamides 10 and 16. Reaction
with chloro- or fluoroformates yields the carbamic
acid ester derivatives 11 and 17.

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SYNTHETIC SCHEME 15c

NC—CH$_2$—CO—NH—(CH$_2$)$_c$—CH$_2$—C$_6$H$_5$

8

↓ gramine

NC—CH—CO—NH—(CH$_2$)$_c$—CH$_2$—C$_6$H$_5$ +   NC—C—CO—NH—(CH$_2$)$_c$—CH$_2$—C$_6$H$_5$

12   **13**

↓ H$_2$ Raney-Ni   ↓ H$_2$ Raney-Ni

H$_2$N—CH—CO—NH—(CH$_2$)$_c$—CH$_2$—C$_6$H$_5$

10

H$_2$N—C—CO—NH—(CH$_2$)$_c$—CH$_2$—C$_6$H$_5$

16

↓ R^1—O—CO—Cl

R^1—O—CO—NH—CH$_2$—CH—CO—NH—(CH$_2$)$_c$—CH$_2$—C$_6$H$_5$

11

↓ R^1—O—CO—Cl

R^1—O—CO—NH—CH$_2$—C—CO—NH—(CH$_2$)$_c$—CH$_2$—C$_6$H$_5$

17
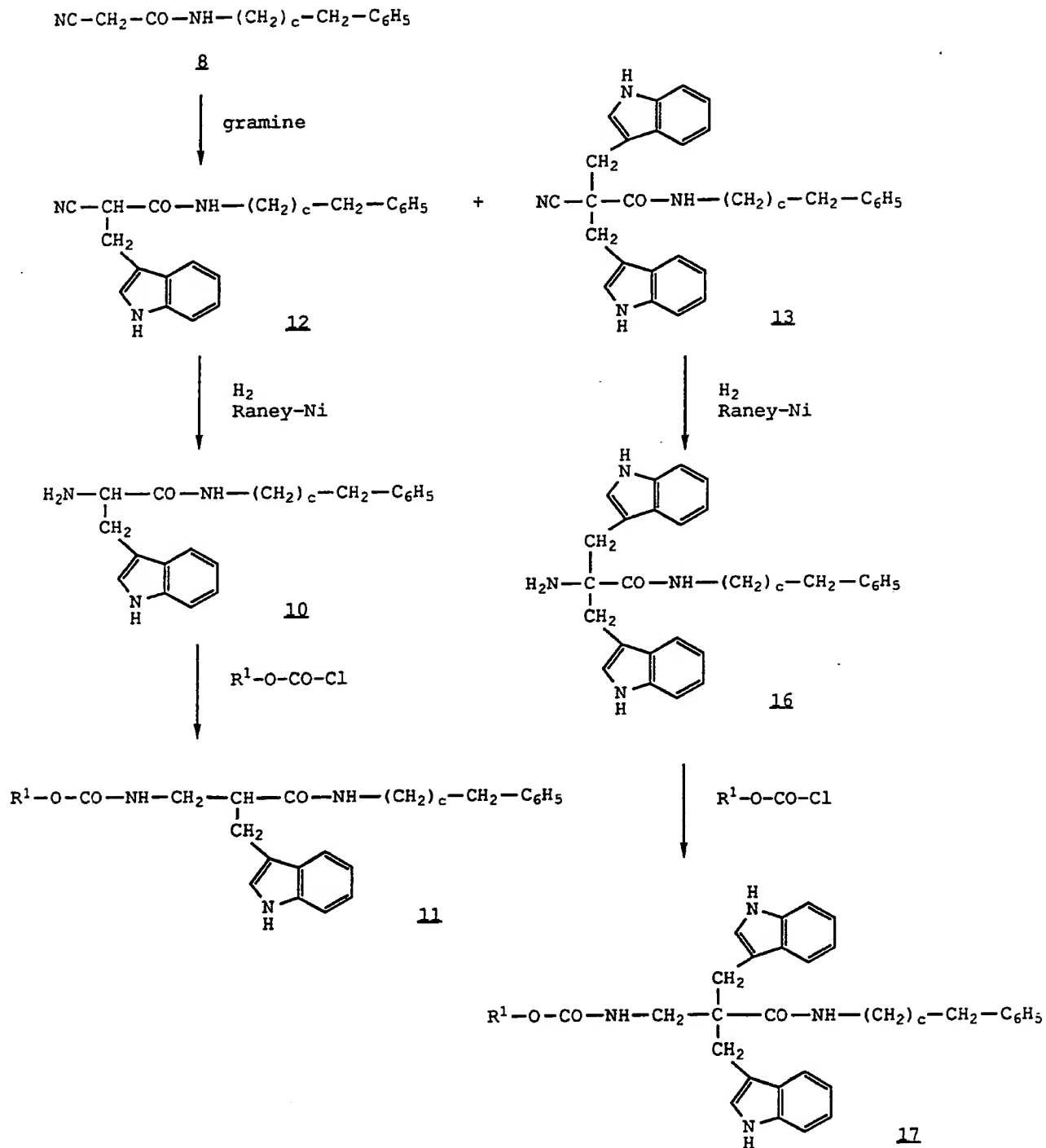
-64-

Scheme 16:

Compounds of the general formula Ib,

$$R^1-CO-NH-CH_2-\underset{\underset{CH_2}{|}}{\overset{\overset{R^2}{|}}{C}}-CO-NH-(CHR^3)_c-CHR^4-Ar \qquad Ib$$
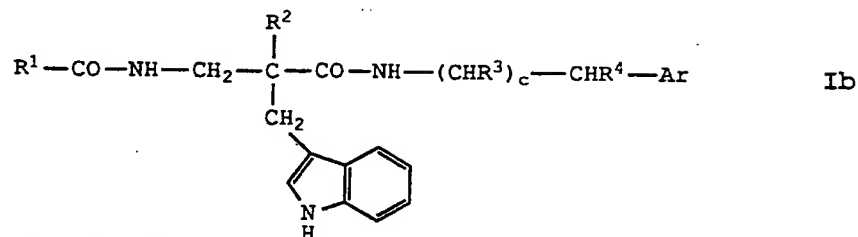
where R^1, R^2, R^3, R^4, and c are as defined above are
prepared according to Synthetic Scheme 16.
Aminoesters 3 are reacted with carboxylic acid
chlorides to give the amides 18. The ester groups of
compounds 18 are hydrolyzed with lithium hydroxide to
the carboxylic acids 19, which are converted to
activated esters, e.g., with pentafluorophenol and
dicyclohexylcarbodiimide to the pentafluorophenyl
esters. The activated esters are reacted with an
appropriate amine to an amide of formula 20. Further
conversions at R^3 and R^4 are done in analogy to known
methods.

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SYNTHETIC SCHEME 16

$$H_2N-CH_2-\underset{\underset{CH_2}{|}}{\overset{\overset{R^2}{|}}{C}}-CO_2Et \quad \xrightarrow{\text{R}^1\text{-CO-Cl}} \quad R^1-CO-NH-CH_2-\underset{\underset{CH_2}{|}}{\overset{\overset{R^2}{|}}{C}}-CO_2Et$$

3   **18**

$$\xrightarrow{\text{LiOH}} \quad R^1-CO-NH-CH_2-\underset{\underset{CH_2}{|}}{\overset{\overset{R^2}{|}}{C}}-CO_2H \quad \longrightarrow$$

19

$$R^1-CO-NH-CH_2-\underset{\underset{CH_2}{|}}{\overset{\overset{R^2}{|}}{C}}-CO-NH-(CHR_3)_c-CHR^4-Ar$$

20
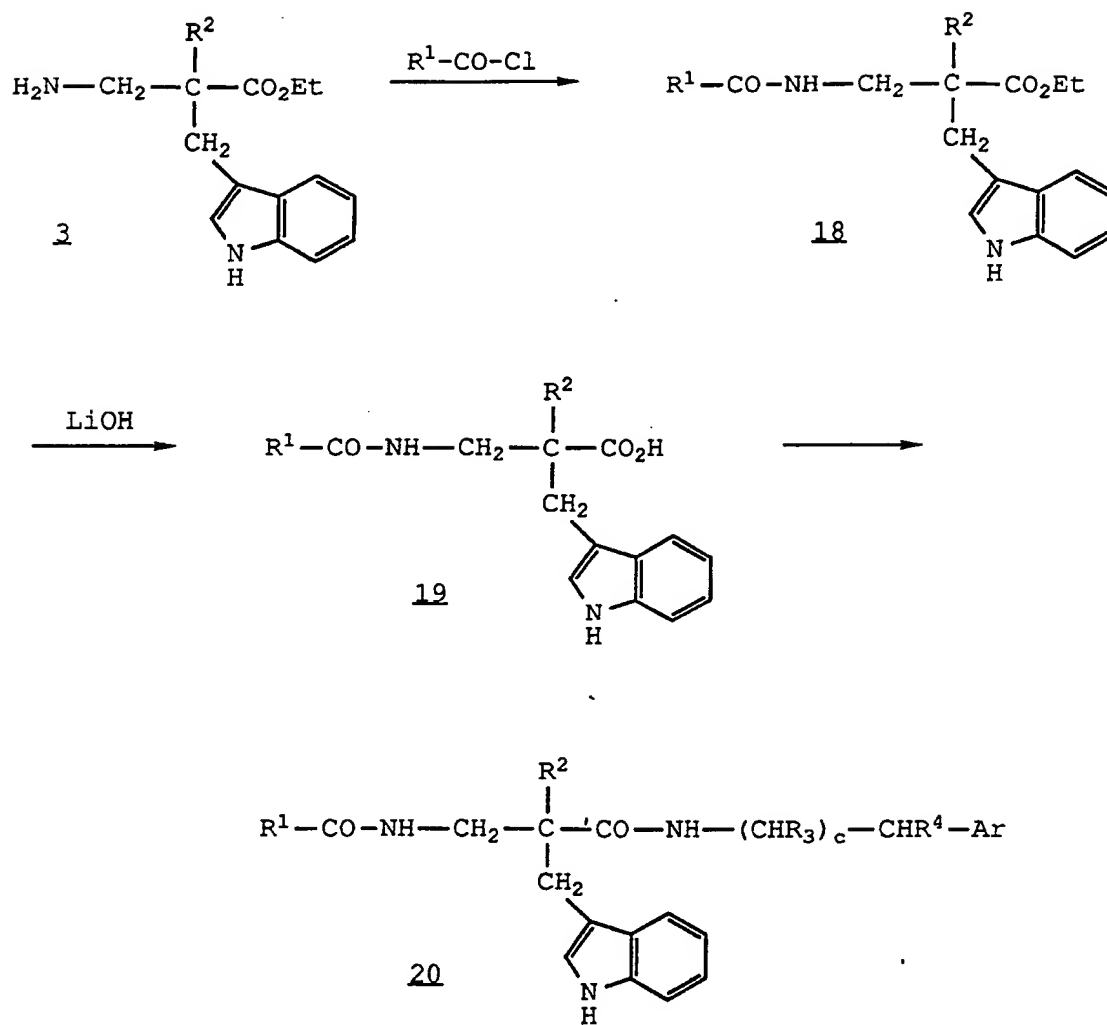
-66-

Scheme 17

Compounds of general formula Ic,

$$R^1—O—CO—NH—\underset{\underset{\underset{CH_2}{|}}{\overset{\underset{CH_2}{|}}{\underset{|}{C}}}{\overset{R^2}{|}}—CO—NH—(CHR^3)_c—CHR^4—Ar$$

Ic
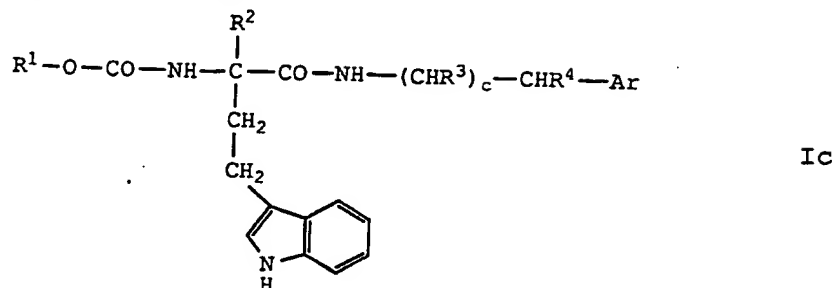
are prepared to <u>Synthetic Scheme 17</u>.

5   1-(3'-indolyl)-butan-3-one is converted with potassium
     cyanide and ammonium carbonate in a Bucherer synthesis
     to the hydantoin <u>21</u>, which is hydrolyzed with aqueous
     sodium hydroxide to the amino acid <u>22</u>, which is
     consequently esterified with methanol and hydrogen
10   chloride to <u>23</u>. Compound 23 is reacted with chloro-
     or fluoroformates to the carbamic acid esters <u>24</u>. The
     ester groups of compounds <u>24</u> are hydrolyzed with
     lithium hydroxide to the carboxylic acids <u>25</u>.
     Acids <u>25</u> are converted to activated esters, e.g., with
15   pentafluorophenol and dicyclohexylcarbodiimide to the
     pentafluoro phenyl esters. The activated esters are
     reacted with an appropriate amine to an amide of
     formula 26. Further conversions at R^3 or R^4 are done
     in analogy to known methods.

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SYNTHETIC SCHEME 17
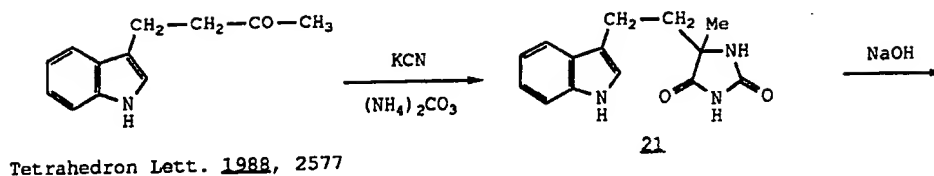
Tetrahedron Lett. 1988, 2577
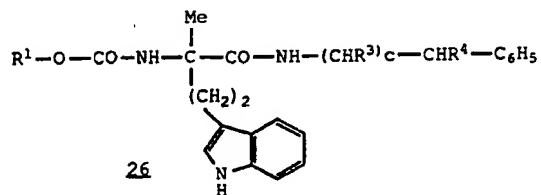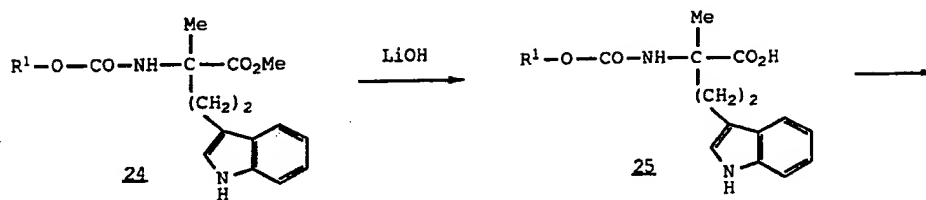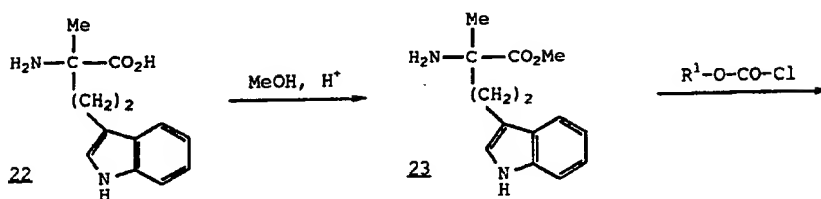
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Scheme 18

Compounds of general formula Id,

$$R^1-O-CO-NH-(CH_2)_2-\underset{\underset{\overset{|}{CH_2}}{\overset{|}{C}}}{\overset{R^2}{C}}-CO-NH-(CHR^3)_c-CHR^4-C_6H_5 \qquad Id$$
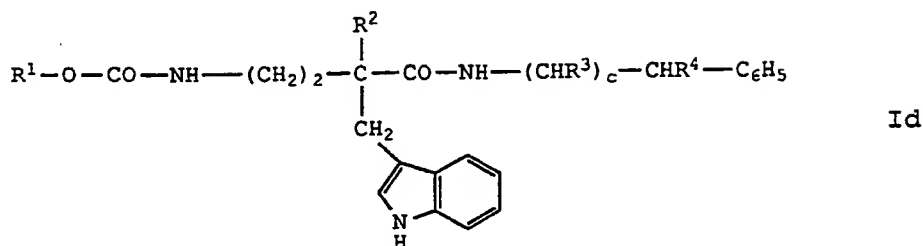
where R^1, R^3, R^4, and c are as defined above and R^2 =
Me are prepared according to Synthetic Scheme 18.
Diethyl methylmalonate 27 is alkylated with gramine
and a base, e.g., NaOH in toluene, to compound 28 by
known methods. The diester 28 is hydrolyzed with
potassium hydroxide to the mono acid 29. The ester
group of 29 is selectively reduced with borane methyl
sulfide complex to compound 30, which is esterified
with methanol and sulfuric acid to the methyl
ester 31. The hydroxy compound 31 is reacted with
p-toluene-sulfonyl chloride and pyridine to the
tosylate 32. Nucleophilic substitution with potassium
cyanide gives the cyanoester 33, which is hydrogenated
catalytically with Raney nickel alloy to the amino
ester 34. The amino ester 34 is reacted with chloro-
or fluoroformates to the carbamic acid esters 35. The
ester groups of compounds 35 are hydrolyzed with
lithium hydroxide to the carboxylic acids 36, which
are converted to activated esters, e.g., with
pentafluorophenol and dicyclohexylcarbodiimide to the
pentafluorophenyl esters. The activated esters are
reacted with an appropriate amine to an amide of
formula 37. Further conversions at R^3 and R^4 are done
in analogy to known methods.

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SYNTHETIC SCHEME 18
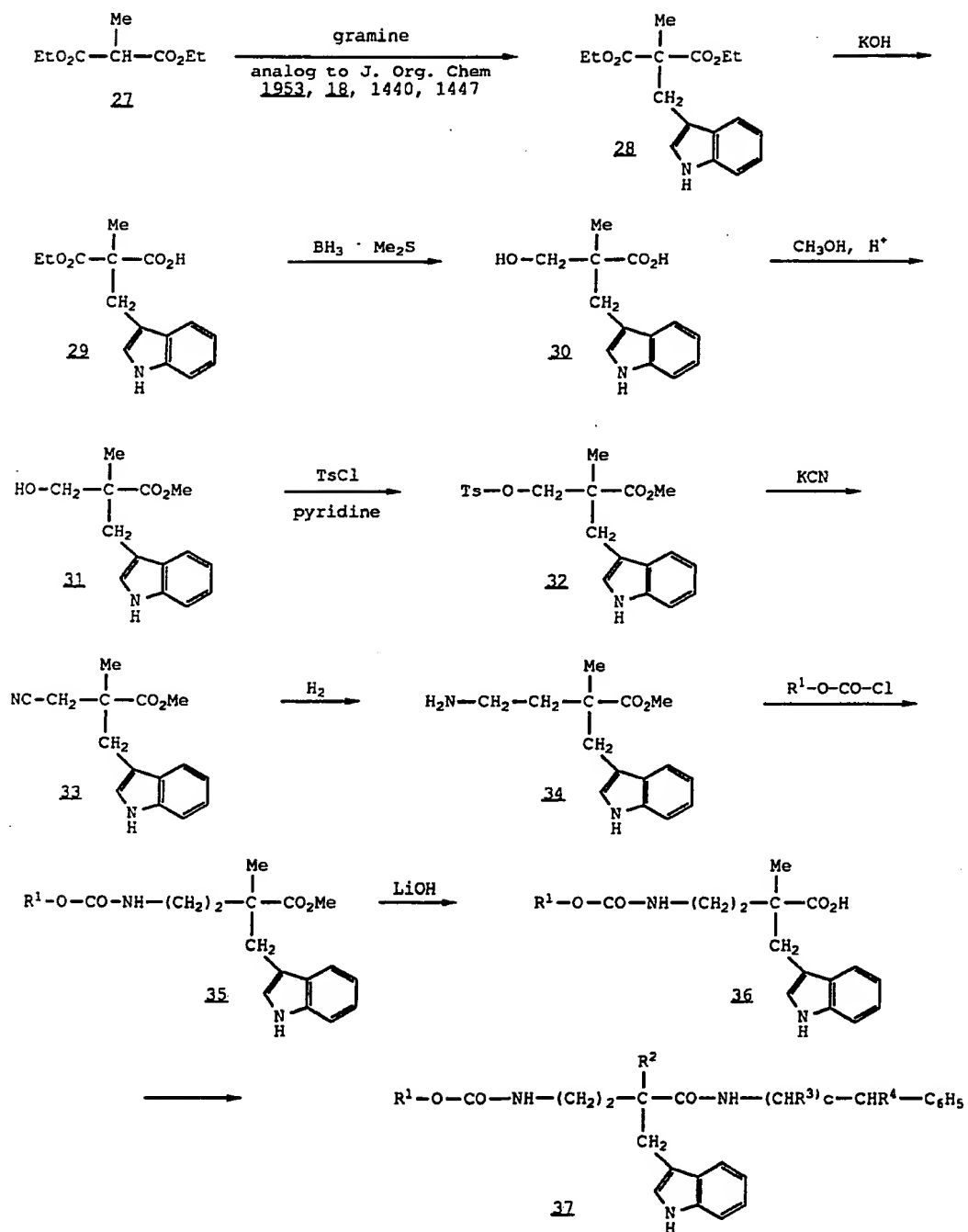
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SYNTHETIC SCHEME 19
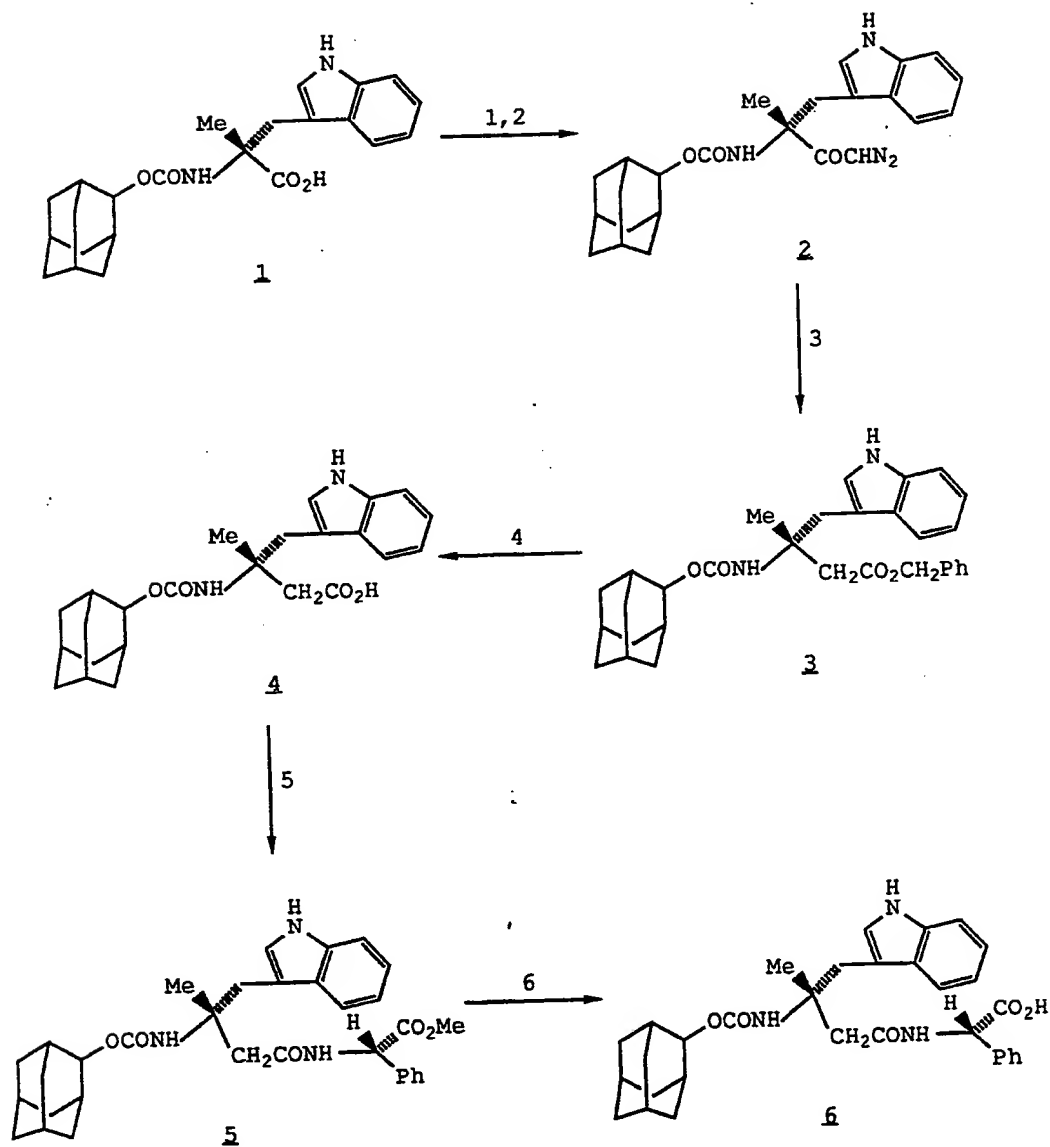
Reagents: 1) N-Methylmorpholine, iBuOCOCl; 2) CH₂N₂;
3) AgOCOPh, HOCH₂Ph, AgOCH₂Ph, 4) H₂Pd/C; 5) DPP, DCCi,
Phenylglycine Methylester; 6) CiOH

SYNTHETIC SCHEME 20
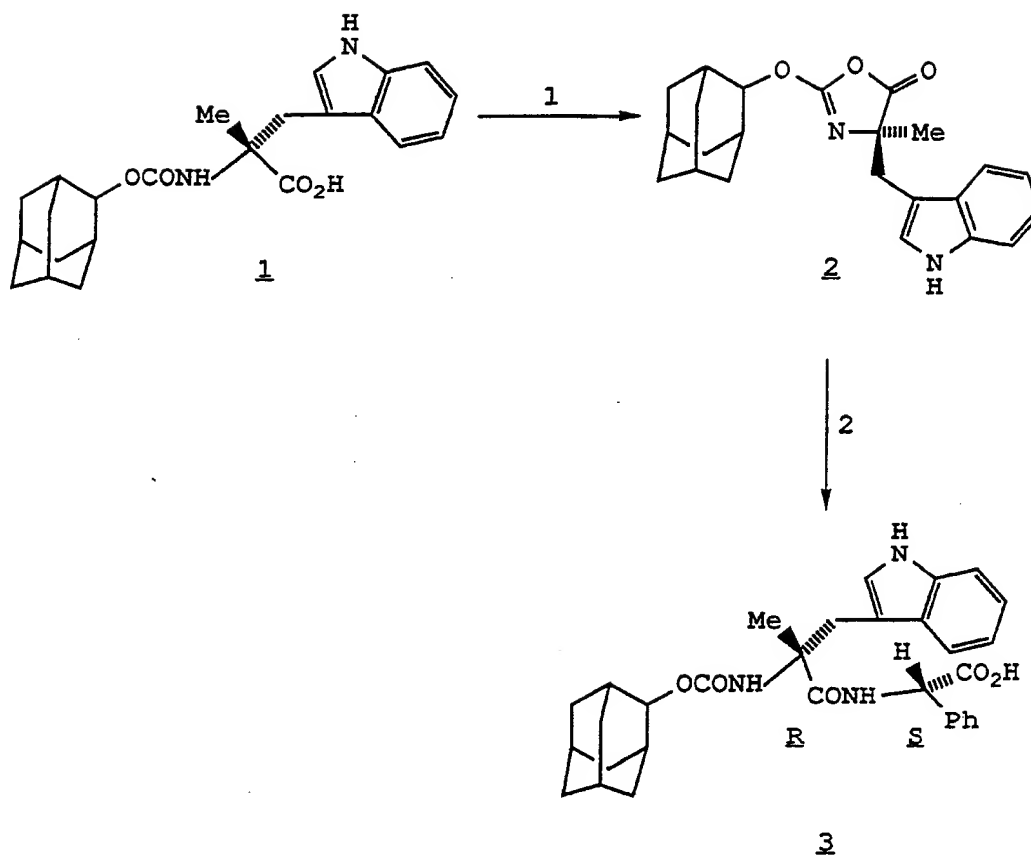
Reagents: 1) DCCi, DMF; 2) Phenylglycine, DMF

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SYNTHETIC SCHEME 21

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SYNTHETIC SCHEME 22

1) pentafluorophenol

2) (S)-Phe-ol

5

6 (71%)

1) t-BuMe₂SiCl   (75%)

2) Lawesson's   (21%)
   Reagent

9
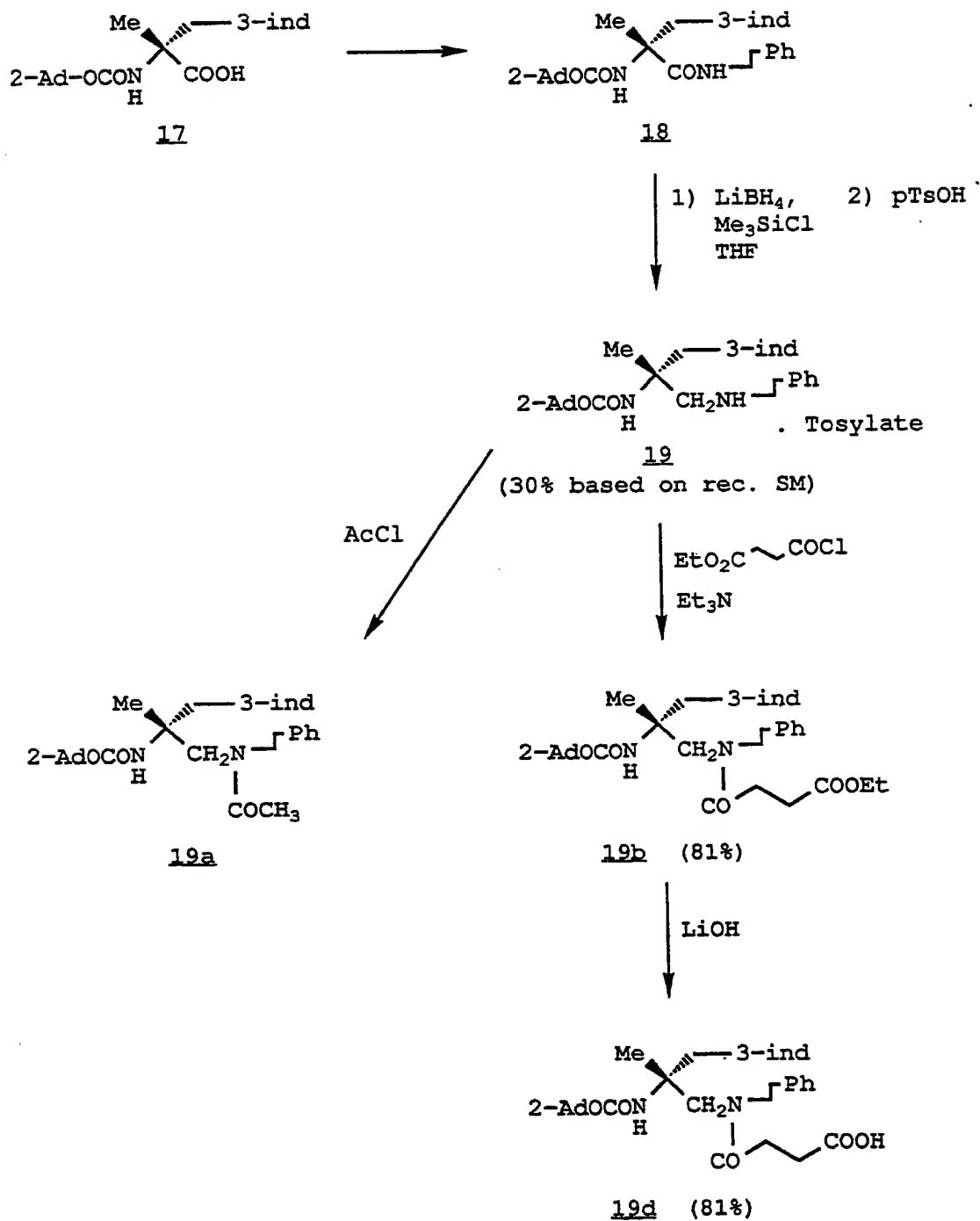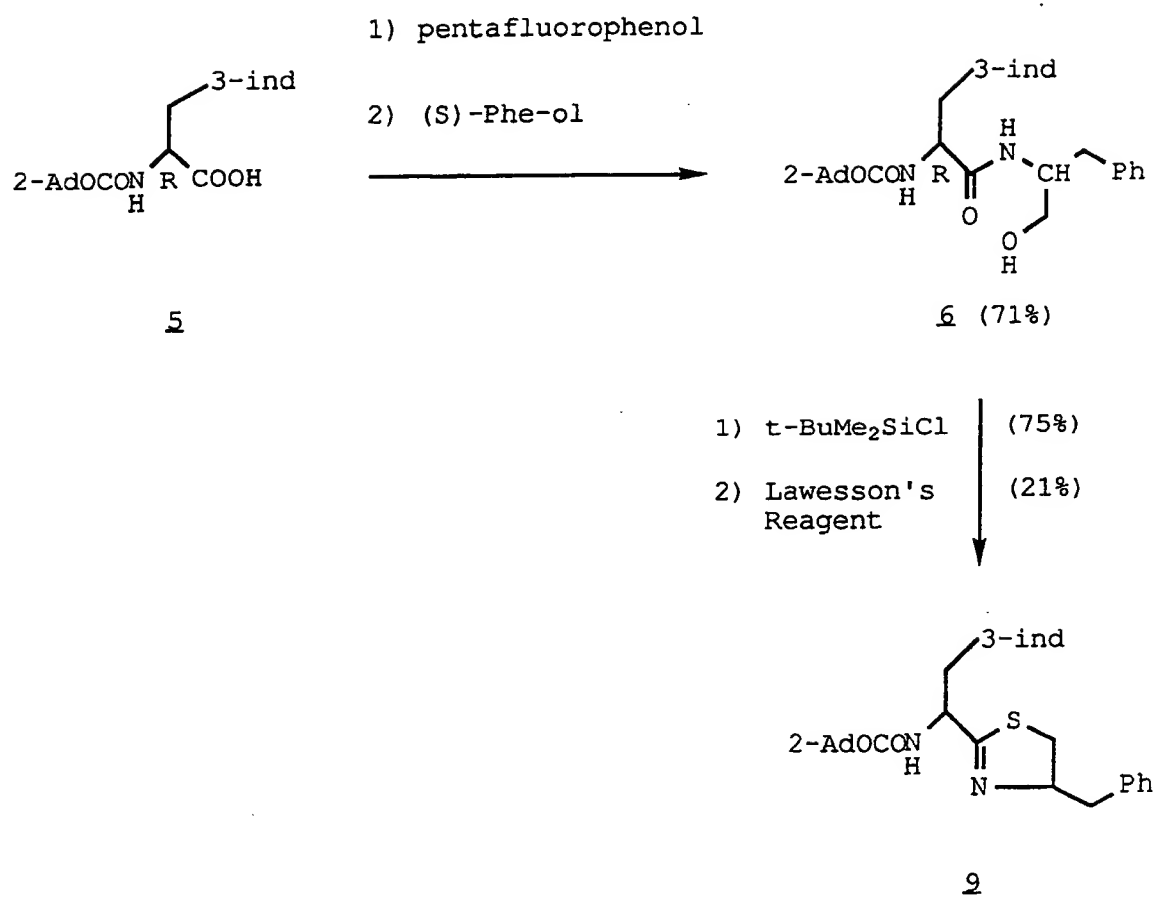
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SYNTHETIC SCHEME 23

(See Examples 97-102)
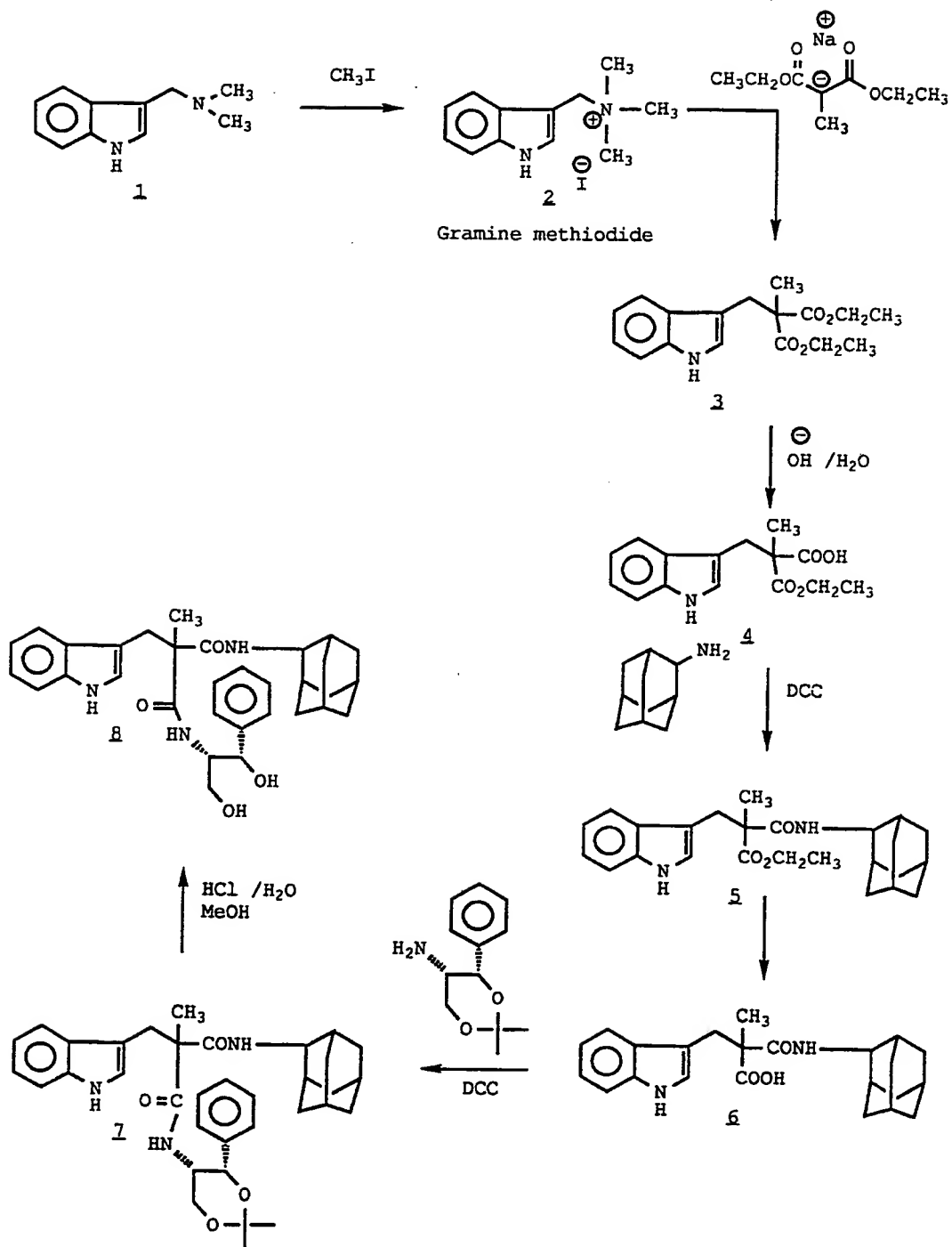
SYNTHETIC SCHEME 23 (cont)
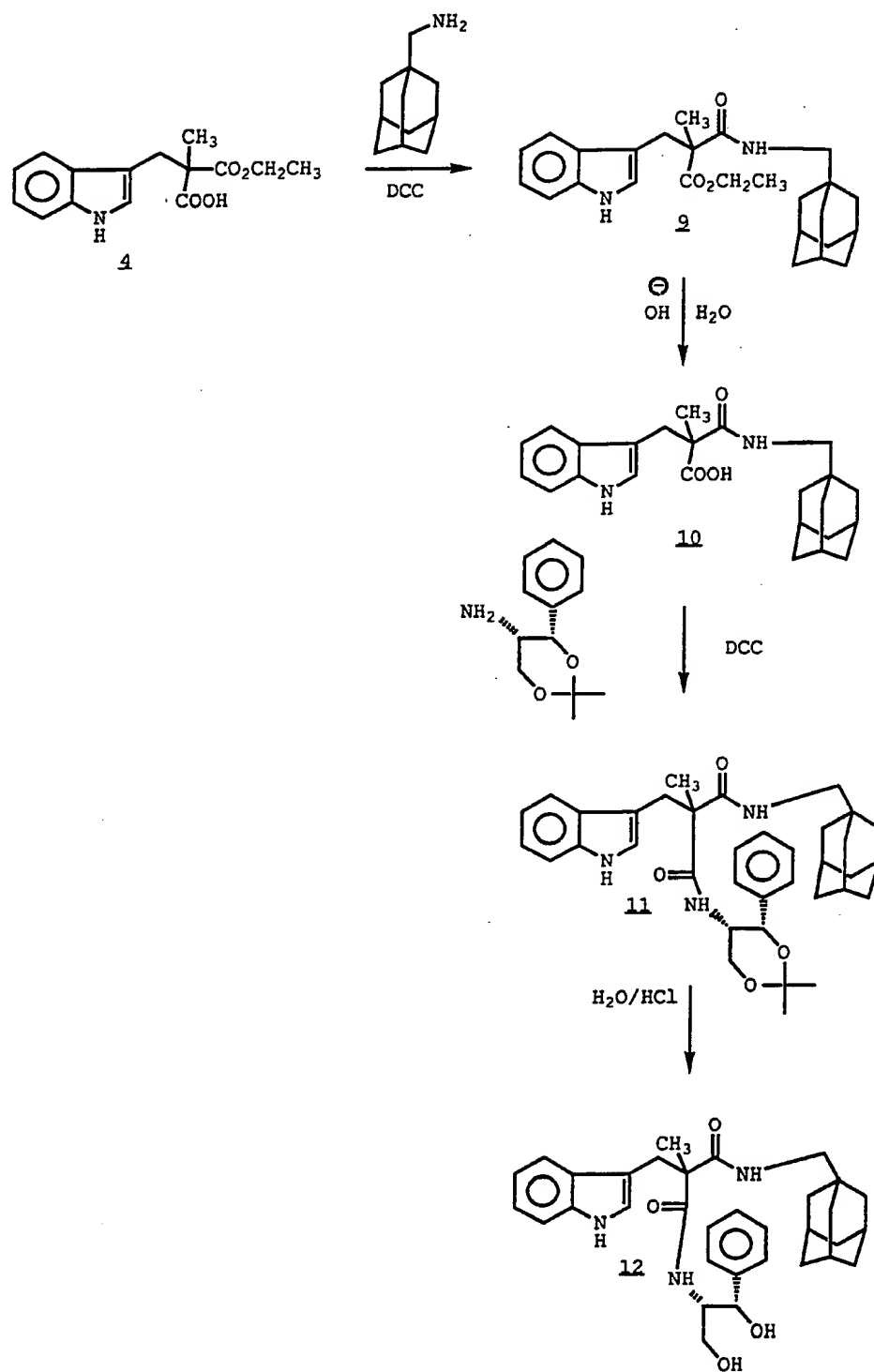
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SYNTHETIC SCHEME 23 (cont)
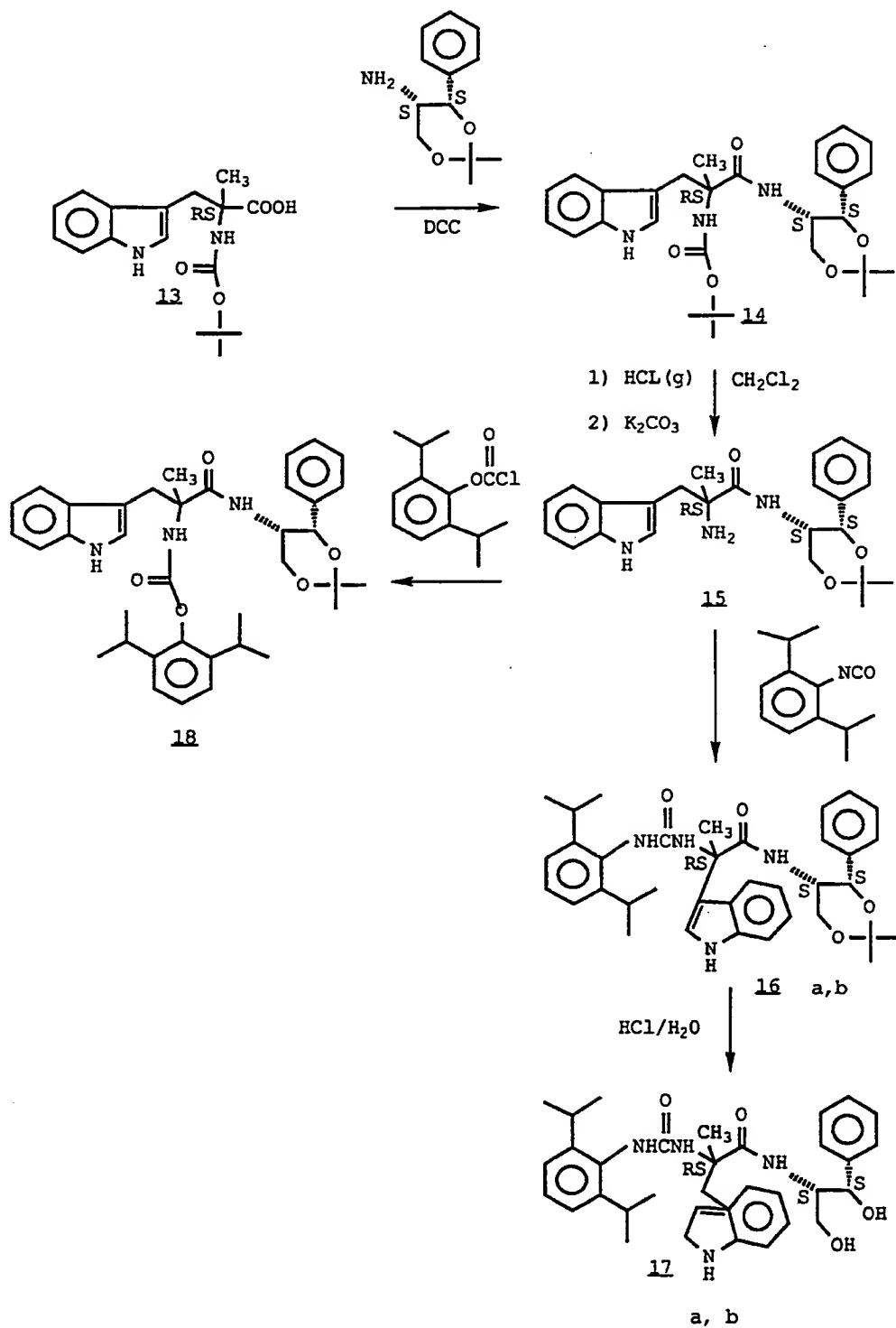
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SYNTHETIC SCHEME 23 (cont)
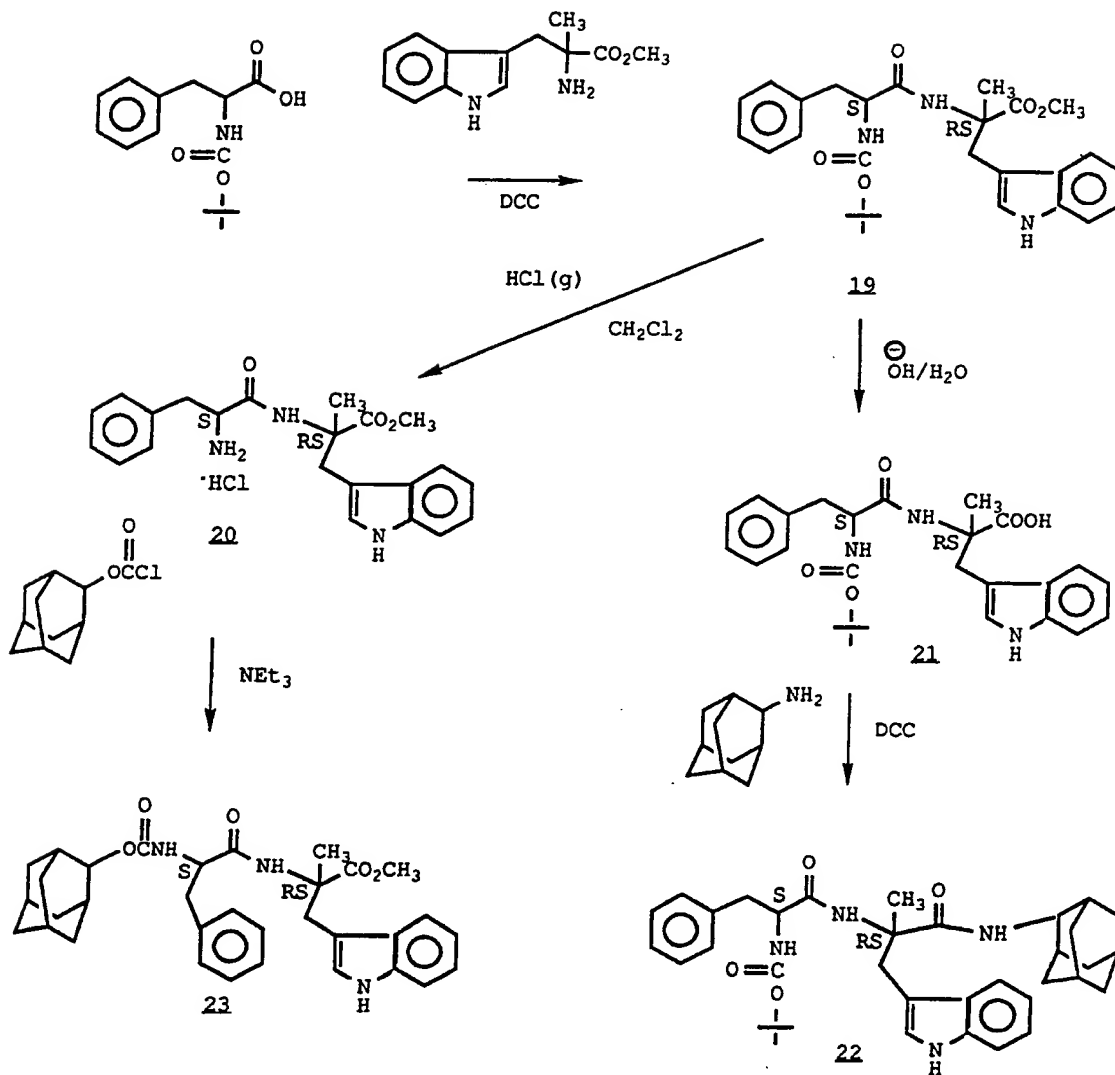
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The biological activity of compounds of the
present invention was evaluated employing an initial
screening test which rapidly and accurately measured
the binding of the tested compound to known CCK

5   receptor sites. Specific CCK receptors have been
shown to exist in the central nervous system. (See
Hays et al, Neuropeptides 1:53-62, 1980; and Satuer et
al, Science 208:1155-1156, 1980).

In this screening test, the cerebral cortices

10   taken from male CFLP mice weighing between 30-40 g
were dissected on ice, weighed, and homogenized in
10 volumes of 50 mM Tris-HCl buffer (pH 7.4 at 0-4°C).
The resulting suspension was centrifuged, the
supernate was discarded, and the pellet was washed by

15   resuspension in Tris-HCl buffer followed by
recentrifugation. The final pellet was resuspended in
20 volumes of 10 nM Hepes buffer (pH 7.2 at 23°C)
containing 130 mM NaCl, 4.7 nM KCl, 5 nM $MgCl_2$, 1 nM
EDTA, 5 mg/mL bovine albumin, and bacitracin

20   (0.25 mg/mL).

In saturation studies, cerebral cortical
membranes were incubated at 23°C for 120 minutes in a
final volume of 500 μL of Hepes incubation buffer
(pH 7.2) together with 0.2-20 nM tritiated-

25   pentagastrin (Amersham International, England).

In the displacement experiments, membranes were
incubated with a single concentration (2 nM) of
ligand, together with increasing concentrations (10^{-11}
to 10^{-14}M) of competitive test compound. In each case,

30   the nonspecific binding was defined as that persisting
in the presence of the unlabeled octapeptide CCK_{26-33}
(10^{-6}M).

Following incubation, radioactivity bound to
membranes was separated from that free in solution by

35   rapid filtration through Whatman GF/B filters and

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washed three times with 4 mL of ice cold Tris-HCl
buffer. Filters from samples incubated with
tritiated-pentagastrin were placed in polyethylene
vials with 4 mL of scintillation cocktail, and the
5   radioactivity was estimated by liquid scintillation
spectrometry (efficiency 47-52%).

The specific binding to CCK receptor sites was
defined as the total bound tritiated-pentagastrin
minus the amount of tritiated-pentagastrin bound in
10   the presence of 10^{-6} octapeptide, CCK_{26-33}.

Saturation curves for specific tritiated-
pentagastrin binding to mouse cortical membranes were
analyzed by the methods of Scatchard (Ann. New York
Acad. Sci. 51:660-672, 1949, and Hill (J. Physiol.
15   40:IV-VIII, 1910), to provide estimates for the
maximum number of binding sites (B_{max}) and the
equilibrium dissociation constant (K_a).

In displacement experiments, inhibition curves
were analyzed by either logit-log plots or the
20   iterative curve fitting computer program ALLFIT
(DeLean, Munson and Redbard, 1978) to provide
estimates of the IC_{50} and nH (apparent Hill
coefficient) values). (IC_{50} values were defined as
the concentration of test compound required to produce
25   50% inhibition of specific binding.)

The inhibition constant (K_i) of the test compound
was then calculated according to the Cheng-Prusoff
equation:

$$K_i = \frac{IC_{50}}{1 + [L]/K_a}$$

30   where [L] is the concentration of radiolabel and K_a is
the equilibrium dissociation constant.

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The K_i values for several representative compounds of the present invention are present in Table III.

The utility of the compounds of the present invention as appetite suppressants is tested according to the procedure described hereinbelow.

In the Palatable Diet Feeding assay, adult male Hooded Lister rats weighing between 200-400 g are housed individually and trained to eat a palatable diet. This diet consists of Nestlés sweetened condensed milk, powdered rat food and rat water which when blended together set to a firm consistency. Each rat is presented with 20-30 g of the palatable diet for 30 minutes per day during the light phase of the light-dark cycle over a training period of five days. The intake of palatable diet is measured by weighing the food container before and after the 30-minute access period (limits of accuracy 0.1 g). Care is taken to collect and correct for any spillage of the diet. Rats are given free access to pellet food and water except during the 30-minute test period.

After the training period, dose-response curves are constructed for CCK8 and several representative compounds of the present invention (n = 8-10 rats per dose level). MPE_{50} values (±95% confidence limits) are obtained for the anorectic effects of these compounds and are shown in Table III.

In therapeutic use as appetite suppression agents, the compounds of the instant invention are administered to the patient at dosage levels of from about 200 to about 2800 mg per day.

Table III below shows the binding data for

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TABLE III

Binding Data on Cerebral Cortexes Taken From Male CFLP Mice	
Example Number	Binding to Central CCK Receptors Ki (nM)
1	11500
3 Isomer 1	1230
3 Isomer 2	780
5	220
6	200
7	374
8	318
14	NT
9	808
11	260
10	39
2	1120
4	NT
19	353
20	493
21	>100
22	704
35	540
34	560
32	103
26	92
24	1100
31	1200
27	910
28	1400
29	240
30	$>10^4$
25	550
33	22
23	800
37	NT
36	50
39	NT
17	

NT = Not tested

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Male Hooded Lister rats (175-250 g) are housed
individually and are caused to fast overnight (free
access to water). They are anesthetized with urethane
(1.5 g/kg IP) and the trachea cannulated to aid
5   spontaneous respiration. The stomach is perfused
continuously using a modification of the original
method of Ghosh & Schild in "Continuous recording of
acid secretion in the rat", Brit. J. Pharmac. 13:54-
61, 1956 as described by Parsons in "Quantitative
10   studies of drug-induced gastric acid secretion".
(Ph.D. Thesis, University of London, 1969). The
cavity of the stomach is perfused at a rate of
3 mL/min with 5.4% w/v glucose solution through both
the esophageal and body cannula. The fluid is
15   propelled by a roller pump (Gilson, Minipuls 2),
through heating coils to bring its temperature to
37 ± 1°C. The perfusion fluid is collected by the
fundic collecting funnel and passed to a pH electrode
connected to a Jenway pH meter (PHM6). An output is
20   taken from the pH meter to a Rikadenki chart recorder
for the on-line recording of the pH of the gastric
perfusate.
Pentagastrin is stored as a frozen aliquot and
diluted to the required concentrations with sterile
25   0.9% w/v NaCl. Novel compounds are dissolved in
sterile 0.9% w/v NaCl on the day of the experiment.
Drugs are administered IV through a cannulated jugular
vein as a bolus in a dose volume of 1 mL/kg washed in
with 0.15 mL 0.9% w/v NaCl. Basal pH is allowed to
30   stabilize before administration of compounds is begun.
Typically 30 minutes elapses between surgery and the
first compound administration.
The compounds of the instant invention are also
useful as antiulcer agents as discussed hereinbelow.

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Aspirin-induced gastric damage is assessed in groups of 10 rats each.

All animals are made to fast for 24 hours before and during the experiment. Drug or vehicle is given 10 minutes before an oral dose of 1 mL of a 45-mg/mL suspension of aspirin in 0.5% carboxymethylcellulose (CMC).

The animals are sacrificed 5 hours after aspirin administration and the stomachs removed and opened for examination.

Gastric damage is scored as follows:

Score

1	Small hemorrhage
2	Large hemorrhage
3.	Small ulcer
4	Large ulcer
5	Perforated ulcer

The specific dosages may, however, be varied depending upon the patient, the severity of the condition being treated, and the activity of the compound employed. Determination of optimum dosages is within the skill of the art.

The compounds of the instant invention are also useful as anxiolytic agents as described and discussed below. Anxiolytic activity is assessed in the light/dark exploration test in the mouse (B. J. Jones, et al, Brit. J. Pharmac. 93:985-993, 1988).

The apparatus used is an open-topped box, 45 cm long, 27 cm wide, and 27 cm high, divided into a small (2/5) area and a large (3/5) area by a partition that extended 20 cm above the walls. There is a 7.5 x 7.5 cm opening in the partition at floor level. The small compartment is painted black and the large compartment white. The floor of each compartment is marked into 9 cm squares. The white compartment is

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illuminated by a 100-watt tungsten bulb 17 cm above
the box and the black compartment by a similarly
placed 60-watt red bulb. The laboratory is
illuminated with red light.

5   All tests are performed between 13 hundred hours,
0 minutes and 18 hundred hours, 0 minutes. Each mouse
is tested by placing it in the center of the white
area and allowing it to explore the novel environment
for five minutes. Its behavior is recorded on

10   videotape and the behavioral analysis is performed
subsequently from the recording. Five parameters are
measured: the latency to entry into the dark compart-
ment, the time spent in each area, the number of
transitions between compartments, the number of lines

15   crossed in each compartment, and the number of rears
in each compartment.

         In this test an increase in the time spent in the
light area is a sensitive measure of, that is directly
related to, the anxiolytic effects of several standard

20   anxiolytic drugs. Drugs were dissolved in water or
saline and administered either subcutaneously,
intraperitoneally, or by mouth (PO) via a stomach
needle.

         The compounds of the instant invention are useful

25   as antipsychotic agents and can be tested for their
ability to reduce the effects of intra-accumbens
amphetamine in the rat as described hereinafter.

         Male Sprague Dawley (CD) Bradford strain rats are
used. The rats are housed in groups of five at a

30   temperature of $21 \pm 2°C$ on a 12 hour light-dark cycle
of lights-on between 07 hours 00 minutes and
20 hours 00 minutes. Rats are fed CRM diet (Labsure)
and allowed water ad libitum.

         Rats are anesthetized with chloral hydrate

35   (400 mg/kg SC) and placed in a Kopf stereotaxic frame.

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Chronically indwelling guide cannulae (constructed of
stainless steel tubing 0.65 mm diameter held
bilaterally in Parspex holders) are implanted using
standard stereotaxic techniques to terminate 3.5 mm
5   above the center of the nucleus accumbens (Ant. 9.4,
Vert. 0.0, Lat. 1.6) or 5.0 mm above the central
nucleus of the amygdala (Ant. 5.8, Vert. -1.8,
Lat. ±4.5) (atlas of De Groot, 1959). The guides are
kept patent during a 14-day recovery period using
10 stainless steel stylets, 0.3 mm diameter, which
extended 0.5 mm beyond the guide tips.

Rats are manually restrained and the stylets
removed. Intracerebral injection cannulae, 0.3 mm
diameter, are inserted and drugs delivered in a volume
15 of 0.5 μL over 5 seconds (a further 55 seconds was
allowed for deposition) from Hamilton syringes
attached via polythene tubing to the injection units.
Animals Are used on a single occasion only.

Behavioral experiments are conducted between
20 07 hours 30 minutes and 21 hours 30 minutes in a quiet
room maintained at 22 ± 2°C. Rats are taken from the
holding room and allowed 1 hour to adapt to the new
environment. Locomotor activity is assessed in
individual screened Perspex cages (25 x 15 x 15 cm
25 (high) (banked in groups of 30) each fitted with
one photocell unit along the longer axis 3.5 cm from
the side; this position has been found to minimize
spurious activity counts due to, for example, preening
and head movements when the animal is stationary.
30 Interruptions of the light beam are recorded every
5 minutes. At this time animals are also observed for
the presence of any nonspecific change in locomotor
activity, e.g., sedation, prostration, stereotyped
movements, that could interfere with the recording of
35 locomotor activity.

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The abilities of the compounds of the invention to inhibit the hyperactivity caused by the injection of amphetamine into the nucleus accumbens of the rat are measured.

An increase in locomotor activity followed the bilateral injection of amphetamine (20 µg) into the nucleus accumbens; peak hyperactivity (50 to 60 counts 5 minutes^{-1}) occurs 20 to 40 minutes after injection. This test is known to be predictive of antipsychotic activity (Costall, Domeney & Naylor & Tyers, Brit. J. Pharmac. 92:881-894).

The compounds of the instant invention prevent and treat the withdrawal response produced when chronic treatment by a drug is stopped or when alcohol abuse is stopped. These compounds are therefore useful as therapeutic agents in the treatment of chronic drug or alcohol abuse as discussed and described below.

The effect of the compounds of the instant invention is illustrated, for example, in the mouse "light/dark box" test wherein five animals are given nicotine, in a range of 0.1 to 100 mg/kg i.p. b.d. for 14 days. After a 24-hour withdrawal period, compound (20) is given at 1.0 mg/kg i.p. b.d. The increased time spent in the light area is a sensitive measure of the effect of compound (20) as an agent to treat withdrawal effects from nicotine.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders,

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or tablet disintegrating agents; it can also be an
encapsulating material.

   In powders, the carrier is a finely divided solid
which is in a mixture with the finely divided active
component. In tablets, the active component is mixed
with the carrier having the necessary binding
properties in suitable proportions and compacted in
the shape and size desired.

   For preparing suppository preparations, a low-
melting wax such as a mixture of fatty acid glycerides
and cocoa butter is first melted and the active
ingredient is dispersed therein by, for example,
stirring. The molten homogeneous mixture is then
poured into convenient sized molds and allowed to cool
and solidify.

   The powders and tablets preferably contain 5% to
about 70% of the active component. Suitable carriers
are magnesium carbonate, magnesium stearate, talc,
lactose, sugar, pectin, dextrin, starch, tragacanth,
methyl cellulose, sodium carboxymethyl cellulose, a
low-melting wax, cocoa butter, and the like.

   Preferred pharmaceutically acceptable salts are
the N-methyl glucamine salt and sodium.

   Pharmaceutically acceptable salts are acetate,
benzenesulfonate, benzoate, bicarbonate, bitartrate,
bromide, calcium acetate, camsylate, carbonate,
chloride, citrate, dihydrochloride, edetate,
edisylate, estolate, esylate, fumarate, glucaptate,
gluconate, glutamate, glycollylarsanilate,
hexylresorcinate, hydrabamine, hydrobromide,
hydrochloride, hydrochloride, hydroxynaphthoate,
iodide, isethionate, lactate, lactobionate, malate,
maleate, mandelate mesylate, methylbromide,
methylnitrate, methylsulfate, mucate, napsylate,
nitrate, pamoate (embonate), pantothenate,

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phosphate/diphosphate, polygalacturonate, salicylate,
stearate, subacetate, succinate, sulfate, tannata,
tartrate, teoclate, triethiodide, benzathine,
chloroprocaine, choline, diethanolamine,
5   ethylenediamine, meglumine, procaine, aluminum,
calcium, lithium, magnesium, potassium, sodium, and
zinc.

The term "preparation" is intended to include the
formulation of the active component with encapsulating
10   material as a carrier providing a capsule in which the
active component (with or without other carriers) is
surrounded by a carrier which is thus in association
with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be
15   used as solid dosage forms suitable for oral
administration.

Liquid form preparations include solutions,
suspensions, and emulsions. Sterile water or water-
propylene glycol solutions of the active compounds may
20   be mentioned as an example of liquid preparations
suitable for parenteral administration. Liquid
preparations can also be formulated in solution in
aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be
25   prepared by dissolving the active component in water
and adding suitable colorants, flavoring agents,
stabilizers, and thickening agents as desired.
Aqueous suspensions for oral use can be made by
dispersing the finely divided active component in
30   water together with a viscous material such as natural
synthetic gums, resins, methyl cellulose, sodium
carboxymethyl cellulose, and other suspending agents
known to the pharmaceutical formulation art.

Preferably the pharmaceutical preparation is in
35   unit dosage form. In such form, the preparation is

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divided into unit doses containing appropriate
quantities of the active component. The unit dosage
form can be a packaged preparation, the package
containing discrete quantities of the preparation, for
5   example, packeted tablets, capsules, and powders in
vials or ampoules. The unit dosage form can also be a
capsule, cachet, or tablet itself, or it can be the
appropriate number of any of these packaged forms.

EXAMPLES

10   EXAMPLE 1
Tricyclo[3.3.1.1^{3,7}]dec-2-yl(R)-[1-(1H-indol-3-yl-
methyl)-2-(methoxymethylamino)-2-oxoethyl]carbamate
(2)

To a solution of acid (1) (859 mg, 2.25 mmol) in
15   dichloromethane (8 mL) was added N-methylmorpholine
(495 μL, 4.50 mmol). The mixture was cooled to -15°C
(CO_2/benzyl alcohol) and isobutylchloroformate
(292 μL, 2.25 mmol) was added. The mixture was
stirred at -15°C for 15 minutes followed by the
20   addition of N,O-dimethylhydroxylamine hydrochloride
(219 mg, 2.25 mmol). The reaction mixture was stirred
at -15°C for 1 hour, then warmed to room temperature
and stirred for a further 15 hours. The mixture was
filtered and the filtrate washed sequentially with
25   sodium hydrogen carbonate, water, 10% citric acid and
brine, dried ($MgSO_4$) and evaporated to dryness. The
crude material was purified by column chromatography
to give hydroxamate (2) (694 mg, 73%) as a white foam;
m.p. 72-80°C. (Found: C, 67.4; H, 7.35; N, 9.8%.
30   $C_{24}H_{31}N_3O_4$ requires C, 67.7; H, 7.3; N, 9.9%); $[\alpha]^{20}$ =
-9.4° (C = 0.3, $CHCl_3$); (S-ISOMER) $[\alpha]^{20}$ = +8.9° (C =
0.3, $CHCl_3$)); υ_{max} (film); 1 695 (CO urethane), 1 657
(CO amide) 741 cm^{-1} (disubstituted Ph); H ($CHCl_3$), δ

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1.30-2.01 (14H, m, adamantyl), 2.99-3.24 (5H, m,
indole CH₂ + NCH₃), 3.58 (3H, s, OCH₃), 4.7 (1H, s,
adamantyl 2-H), 5.00 (1H, br d, C$\underline{\text{H}}$ (NHR)CON⁻), 5.36
(1H br d, urethane NH), 6.92-7.17 (3H, m, indole
2,5,6-H), 7.27 (1H, d, $\underline{J}$ 8 Hz, indole 7-H), 7.53 (1H,
d, $\underline{J}$ 8 Hz, indole 4-H), 7.99 (1H, s, indole NH).

Tricyclo[3.3.1.1^{3,7}]dec-2-yl(R)-[1-formyl-2-(1H-indol-
3-yl)ethyl carbamate (3)

        Lithium aluminum hydride (45 mg, 1.2 mmol) was
added portionwise over a period of 30 minutes to a
solution of the hydroxamate (2) (197 mg, 0.460 mmol)
in THF (3 mL) at 0°C. The mixture was stirred for a
further 30 minutes, then ether (30 mL) was added
followed by an ice cold solution of 10% citric acid
(40 mL). The mixture was stirred vigorously for
30 minutes, then the layers were separated and the
aqueous layer extracted with ether (5 x 10 mL). The
ether extracts were combined and sequentially washed
with saturated sodium hydrogen carbonate (25 mL),
water (25 mL), 10% citric acid (25 mL), and brine
(25 mL), dried (Na₂SO₄) and concentrated in vacuo to
give aldehyde (3) (140 mg, 83%) as a white foam; ν_{max}
(film) 1 725 sh (aldehyde C=O) and 1 693 cm⁻¹
(urethane C=O); H (300 M Hz; CDCl₃), ν1.47-2.13 (14H,
m, adamantyl), 3.26 (2H, d of d, $\underline{J}$ 15 and 7 Hz,
indCH₂), 4.58 (1H, br d, C$\underline{\text{H}}$(NHR)CHO), 4.84 (1H, s,
adamantyl 2-H), 6.98-7.26 (3H, m), 7.35 (1H, d, $\underline{J}$
8 Hz, indole 7-H), 7.60 (1H, br d, $\underline{J}$ 8 Hz, indole
4-H), 8.24 (1H, br s, indole NH), 9.64 (1H, s, CHO).

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Tricyclo[3.3.1.1^{3,7}]dec-2-yl[S-(R)]-[2-[[1-(hydroxy-
methyl)-2-phenylethyl]amino]-1-(1H-indol-
3-ylmethyl)ethyl]carbamate (4), Example 1

Sodium cyanoborohydride (37 mg, 0.59 mmol) was
added portionwise over a period of 15 minutes to a
solution of aldehyde (3) (136 mg, 0.370 mmol) and
(S)-2-amino-3-phenyl propanol (61 mg, 0.40 mmol) in
methanol-acetic acid (99:1) (5 mL). The mixture was
stirred for 2 hours at room temperature then chilled
(ice bath). Saturated sodium hydrogen carbonate
(30 mL) was added with stirring, followed by ethyl
acetate (45 mL). The organic layer was separated,
washed with brine (5 mL), dried (Na$_2$SO$_4$) and
evaporated to dryness. The crude product was purified
by column chromatography (SiO$_2$:dichloromethane-
methanol (95:5) as eluant] to give amino alcohol (4)
(60 mg, 32%) as a beige foam; m.p. 59-61°C. (Found:
C, 73.7; H, 7.8; N, 8.3%. C$_{31}$H$_{39}$N$_3$O$_3$·0.2 H$_2$O requires
C, 73.7; H, 7.9; N, 8.3%); v_{max} (film) 3 325 (OH),
1 690 (CO urethane), 1 496 (N-H), 1 266 (OH), 1 048
(C-O), 740 and 701 cm^{-1} (monosubstituted Ph); H (CDCl$_3$)
δ 1.31-2.04 (16H, m, adamantyl + NH + OH), 2.44-3.01
(7H, m, indCH$_2$, -CH$_2$NH-, CH$_2$Ph, NH-CH(CH$_2$OH)CH$_2$Ph),
3.21 (1H, dd, J 11 and 6 Hz, CH of CH$_2$OH), 3.47 (1H,
dd, J 11 and 4 Hz, CH of CH$_2$OH), 3.97 (1H, m,
-CH$_2$CH(NHCO$_2$R)CH$_2$NH-), 4.66 (1H, br d, urethane NH),
4.73 (1H, s, adamantyl 2-H), 6.87 (1H, d, J 2 Hz,
indole 2-H), 6.96-7.24 (7H, m, indole 5,6-H + Ph),
7.29 (1H, d, J 8Hz, indole 7-H), 7.55 (1H, d, J 7 Hz,
indole 4-H), 7.97 (1H, brs, indole NH).

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EXAMPLE 2

Tricyclo[3.3.1.1^{3,7}]dec-2-yl[S-(S)]-2-[[1-(hydroxy-
methyl)-2-phenylethyl]amino]-1-(1H-indol-3-ylmethyl)-
ethyl]carbamate (5), Example 2

5   Compound 5 (253 mg, 23%) was synthesized using the
same procedure as that described above for
compound (4). White foam, m.p. 62-63°C. (Found: C,
73.3; H, 7.8; N, 8.3%. $C_{31}H_{39}N_3O_3 \cdot 0.4\ H_2O$ requires C,
73.2; H, 7.9; N, 8.3%). v_{max} (film) 3 331 (OH), 1 692
10   (CO urethane), 1 513 (N-H), 1360 (O-H), 1048 (C-O),
739 and 701 cm^{-1} (monosubstituted Ph); H (CDCl$_3$), δ
1.47-2.10 (16H, m, adamantyl + NH + OH), 2.54-3.04
(7H, m, CH^2 indole, CH$_2$NH, CH$_2$Ph + CH$_2$CH(CH$_2$OH)CH$_2$Ph),
3.30 (1H, dd, J 11 and 6 Hz, CH of CH$_2$OH), 3.59 (1H,
15   dd, J 11 and 4 Hz, CH of CH$_2$OH), 4.06 (1H, m,
-CH$_2$CH(NHCO$_2$R)CH$_2$NH-), 4.81 (2H, br s, adamantyl 2-H +
urethane NH), 6.86 (1H, brs, indole 2-H), 7.06-7.32
(7H, m, indole 5,6-H + Ph), 7.35 (1H, d, J 8 Hz,
indole 7-H), 7.59 (1H, d, J 8 Hz, indole 4-H), 8.03
20   (1H, br s, indole NH).

EXAMPLE 3

Tricyclo[3.3.1.1^{3,7}]dec-2-yl-[2-(1H-indol-3-yl)1-
[[[(4-nitrophenyl)methoxy]carbonyl]amino]ethyl]-
carbamate (6)

25   To a solution of acid (1) (3.62 g, 9.74 mmol) in
anhydrous THF (36 mL) at -10°C was added
N-methylmorpholine (1.15 mL, 10.4 mmol) and n-isobutyl
chloroformate (1.35 mL, 10.4 mmol). This mixture was
stirred for 20 minutes at -10°C then filtered.
30   Trimethylsilyl azide [Aldrich] (1.89 mL, 14.2 mmol)
was added to the filtrate and the resulting solution
stirred at -10°C for 1 hour. The solvent was then
removed in vacuo at 25°C and the residue partitioned
between ethyl acetate (100 mL) and saturated sodium

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hydrogen carbonate (100 mL). The layers were
separated and the organic phase was washed with brine,
dried (MgSO$_4$), and concentrated _in vacuo_ at 25°C. The
residue was taken up in toluene (100 mL) and treated

5   at 40°C until rearrangement to the isocyanate was
complete. (IR: υ_{max} N$_3$ 2139, υ_{max} NCO 2249 cm^{-1}).
p-Nitrobenzylalcohol (2.20 g, 14.3 mmol) and DABCO
(149 mg, 1.33 mmol) were added and the mixture left at
40°C for 15 hours. The solvent was removed _in vacuo_

10 and the crude product purified by column
chromatography [SiO$_2$:ether-hexane (4:1) as eluant] to
give (6) (2.12 g, 42%) as a yellow solid which was
recrystallized from ether/hexane, m.p. 148-149°C. ^{1}H
NMR (300 m Hz), δ1.39-2.03 (m 14H, adamantyl), 3.07

15 (brs, 12H, CH$_2$ ind + H$_2$O/HOD), 4.64 (s, 1H, adamantyl
2-H), 5.14 (s, 2H, CH$_2$Ph), 5.37 (m, 1H, C$\underline{H}$
(NHCO$_2$)-NHCO$_2$), 6.90-7.29 (m, 4H, indole H-2, H-5,
H-6, and NH), 7.34 (d, $\underline{J}$ 8 Hz, 2H, H-subst. Ph),
7.46-7.62 (m, 3H, ind H-4, ind H-7, NH), 8.16 (d, $\underline{J}$

20 8 Hz, 2H, 4-subst. Ph), 10.61 (s, 1H, ind NH); IR
(film): 2908 + 2855 (adamantyl), 1703 (br, CO
urethane), 1520 (NO$_2$), 1347 (NO$_2$).
Anal. C$_{29}$H$_{32}$N$_4$O$_6$ requires
        C, 65.40; H, 6.06; N, 10.52.

25 Found: C, 65.25; H, 6.03; N, 10.50.

Tricyclo[3.3.1.1^{3,7}]dec-2-yl[1-[[(1-hydroxymethyl)-
2-phenylethyl]carbonyl]amino]-2-(1H-indol-3-yl)ethyl]-
carbamate
Compound (7), Example 3

30   The urethane (6) (190 mg, 0.357 mmol) in ethyl
acetate (36 mL) was hydrogenated over palladium
hydroxide on carbon (Pearlman's catalyst) at 45 psi
and 30°C for 1 hour. The mixture was filtered through
celite to remove the catalyst into a flask containing

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the HOBT ester of 2-(acetoxymethyl)-3-phenylpropionic
acid [the latter was generated via the reaction of
2-(acetoxymethyl)-3-phenylpropionic acid (81 mg,
0.36 mmol) in ethyl acetate (5 mL) with

5   1-hydroxybenzotriazole (57.5 mg, 0.426 mmol) and DCCI
(85.9 mg, 0.416 mmol) at 0°C for 30 minutes]. The
resulting mixture was stirred at room temperature for
18 hours. The solution was concentrated in vacuo,
chilled (ice-bath), filtered, and evaporated to

10   dryness. the residue was taken up in THF:MeOH:H_2O
(3:2:1) (6 mL), lithium hydroxide monohydrate (28 mg,
0.67 mmol) added, and the mixture stirred at room
temperature for 18 hours. The reaction mixture was
poured into 2N HCl (50 mL) and extracted with ethyl

15   acetate (3 x 25 mL). The organic phase was washed
with saturated NaCl, dried ($MgSO_4$), filtered, and
evaporated to dryness. The crude product was purified
by column chromatography [SiO_2: dichloromethane-
methanol (95:5) as eluant] to given an approximately

20   50:50 mixture of diastereomeric alcohols (7) (16 mg
total, 8%) as yellow oils. Isomer I: TLC Rf = 0.24
(CH_2Cl_2-MeOH (95.5)); ^1H NMR (300 M Hz): δ1.43-2.04
(br m, 17H, adamantyl + H_2O), 2.42 (m, 1H, NHCO, CH),
2.67-3.22 (br m, 5H, CH_2 ind + CH_2Ph + OH), 3.67 (m,

25   2H, CH_2OH), 4.78 (s, 1H, adamantyl H=2), 5.40 (brs,
1H), 5.58 (brs, 1H), 6.26 (brs, 1H, amide NH), 6.82
(s, 1H, ind H-2), 7.02-7.37 (m, 9H, Ph + ind H-5, ind
H-6, ind H-7, + $CHCl_3$), 7.44 (d, J 8 Hz, ind H-4),
8.16 (s, 1H, ind NH); IR (film): 3540-3140 (br, OH),

30   2910 + 2855 (adamantyl), 1695 (urethane Co), 1660
(amide CO); Isomer II: TLC Rf = 0.19 [CH_2Cl_2-MeOH
(95:5); ^1H NMR (300 M Hz): δ1.47-2.08 (m, 17H,
adamantyl + H_2O), 2.42 (m, 1H, NHCO·CH), 2.61-2.97 (m,
3H, CH_2 + OH), 3.19 (d, J 7 Hz, CH_2), 4.68 (brs, 2H,

35   CH_2OH), 4.75 (s, 1H, adamantyl H-2), 5.18 (brs, 1H),

5.49 (brs, 1H), 6.30 (brs, 1H, amide NH), 6.96 (s, 1H,
ind H-2), 7.02-7.30 (m, 9H, Ph + ind H-5, ind H-6 +
CHCl$_3$), 7.37 (d, $\underline{J}$ 8 Hz, 1H, ind H-7), 7.57 (d, $\underline{J}$
8 Hz, 1H, ind H-4), 8.12 (s, 1H, ind NH); IR (film):

5   3520-3160 (br, OH), 2907 + 2855 (adamantyl), 1696
(urethane CO), 1660 (amide CO).

EXAMPLE 4

2-Adamantyloxycarbonyltryptophandiazoketone (8)

Preparation of diazomethane. CAUTION!

10   DIAZOMETHANE IS HIGHLY TOXIC AND EXPLOSIVE (NO GROUND
GLASS JOINTS). HANDLE WITH CARE IN A FUME HOOD.
n-METHYLNITROSUREA IS HIGHLY TOXIC AND CARCINOGENIC.
HANDLE IN A FUME HOOD USING A FULL FACE MASK AND
GLOVES.

15   A solution of 40% potassium hydroxide (4.5 mL,
32 mmol) was added dropwise to a suspension of
N-methylnitrosurea (1.5 g, 15 mmol) in ether (25 mL),
cooled in an ice-salt bath. After all the solid had
dissolved (additional base is added if necessary), the

20   ethereal solution of diazomethane was dried over solid
potassium hydroxide. This drying process was repeated
twice more and the diazomethane used immediately.

          To a solution of 2-adamantyloxycarbonyltryptophan
(1) (1.77 g, 4.61 mmol) in THF (25 mL) at 0°C was

25   added N-methylmorpholine (557 µL, 5.07 mmol) and
isobutylchloroformate (658 µL, 5.07 mmol). The
mixture was stirred for 20 minutes at 0°C, then
filtered. To the filtrate was added a solution of
diazomethane (10 mmoL) in ether (produced from

30   N-methylnitrosurea (1.0 g, 10 mmol)). The resulting
solution was stirred for 15 minutes at 0°C, then for
15 hours at room temperature. The solvent was removed
in vacuo and the residue taken up in ethyl acetate
(100 mL). This solution was washed with water

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(2 x 10 mL), 5% citric acid (2 x 10 mL), 1N NaHCO$_3$
(10 mL), and brine (10 mL). It was dried (MgSO$_4$) and
the solvent removed *in vacuo*. The crude product was
purified by column chromatography [SiO$_2$:hexane-ethyl

5   acetate (5:4) as eluant] to give diazoketone (8)
(1.35 g, 72%) as a yellow foam, m.p. 72-75°C. v^{max}
(CDCl$_3$ film) 2 109 (N$_2$); 1 697 (CO) and 740 cm^{-1}
(disubstituted Ph); H (d$_6$-acetone), δ1.39-2.02 (14H,
m, adamantyl), 3.13 (1H, dd, *J* 15 and 8 Hz, CH of CH$_2$

10   indole), 3.29 (1H, dd, *J* 15 and 5 Hz, CH of
CH$_2$indole), 4.51 (1H, m, CH$_2$CH(NHR)CO), 4.69 (1H, S,
adamantyl 2-H); 5.90 (1H, brs, CHN$_2$); 6.41 (1H, s, NH
CO); 7.01 (1H, t, *J* 7 Hz, indole 5 or 6-H), 7.09 (1H,
t, *J*, 7 Hz, indole 7-H), 7.61 (1H, d, *J* 9 Hz, indole

15   4-H), 10.05 (1H, brs, indole NH).

2-Adamantyloxycarbonyltryptophanyl Chloromethyl Ketone (9)

Hydrochloric acid (11.1 mL of a 0.30 M solution in
dioxane) was added dropwise with stirring to a

20   solution of diazoketone (8) (1.35 g, 3.32 mmol) in THF
(100 mL) at 0°C. The reaction was monitored by
infrared for the disappearance of the N$_2$ peak
(2 109 cm^{-1}) in the starting material. When all the
diazoketone had gone (ca 60 minutes) the reaction

25   mixture was quenched with saturated sodium hydrogen
carbonate (20 mL). The mixture was concentrated *in
vacuo* and the residue partitioned between ethyl
acetate (100 mL) and saturated sodium hydrogen
carbonate (1090 mL). The layers were separated and

30   the aqueous extracted further with ethyl acetate
(2 x 100 mL). The combined ethyl acetate fraction was
washed with brine (50 mL), dried (MgSO$_4$), and the
solvent removed *in vacuo*. The crude product was
recrystallized from ethyl acetate-hexane to give

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<u>chloroketone</u> (9) (1.29 g, 94%), m.p. 138-140°C.
(Found: C, 66.6; H, 6.7; Cl, 8.3; N, 6.9%.
$C_{23}H_{27}ClN_2O_3$ requires C, 66,6; H, 6.6; Cl, 8.5; N,
6.75%). v_{max} (CDCl$_3$ film), 1 740 (CO α chloroketone),
1 698 (CO urethane), and 736 cm^{-1} (disubstituted Ph);
H (CDCl$_3$) δ1.45-2.06 (14H, m, adamantyl), 3.27 (2H, m,
CH$_2$ind), 3.96 (1H, d, $\underline{J}$ 16 Hz, CH of CH$_2$Cl), 4.11 (1H,
d, $\underline{J}$ 16 Hz, CH of CH$_2$Cl), 4.83 (2H, m, CH$_2$CHCO and
adamantyl 2-H), 5.35 (1H, d, $\underline{J}$ 7 Hz, NH), 7.00 (1H, d,
$\underline{J}$ 2 Hz, indole 2-H), 7.14 (1H, t, 6 Hz, indole 5 or
6-H), 7.22 (1H, t, $\underline{J}$ 6 Hz, indole 5 or 6-H), 7.37 (1H,
d, $\underline{J}$ 8 Hz, indole 7-H), 7.61 (1H, d $\underline{J}$ 8 Hz, indole
4-H), 8.20 (1H, s, indole NH).

<u>α-[4-(1H-indole-3-yl)-2-oxo-3-[[(tricyclo[3.3.1.1^{3,7}]-
dec-2-yloxy)carbonyl]amino]butyl]benzene propanoic
acid, Compound (10), Example 4</u>

Sodium iodide (Aldrich) (51 mg, 0.34 mmol) was
added to a solution of chloroketone (126) (112 mg,
0.27 mmol) in anhydrous DME (5 mL) at room
temperature. This mixture was stirred at room
temperature for 15 minutes, then an aliquot (800 µL,
0.30 mmol) of an anion solution [generated by the
reaction of sodium hydride (60% dispersion in oil)
(88 mg, 2.2 mmol) in anhydrous DME (5 mL) with
diethylbenzylmalonate (950 µL, 4.0 mmol) at room
temperature] was added. The resulting solution was
stirred at room temperature for 2 hours. The solvent
was removed <u>in vacuo</u>, the residue taken up in
dichloromethane (50 mL), washed with brine, dried
(MgSO$_4$), and evaporated under reduced pressure. The
crude material was purified by column chromatography
[SiO$_2$:hexane-ethyl acetate (2:1) as eluant] to yield
<u>ketodiester</u> (100 mg, 59%); m.p. 49-54°C. (Found: C,
70.8; H, 7.2; N, 4.4%. $C_{37}H_{44}N_2O_7$ requires C, 70.7; H,

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7.05; N, 4.5%). υ_{max} (CH$_2$Cl$_2$ film) 1 728 cm^{-1} (CO); H
(CDCl$_3$ δ1.42-2.08 (14H, m, adamantyl), 2.98 (1H, d, $\underline{J}$
19 Hz), 3.18 (1H, dd, $\underline{J}$ 15 and 6 Hz, CH$_2$ind), 3.24
(1H, dd, $\underline{J}$ 15, and 6 Hz), CH$_2$ind), 3.34 (2H, s, CH$_2$),

5   4.18 (4H, m, 2 x CH$_2$), 4.62 (1H, m, CH$_2$C$\underline{H}$(CO)NH), 4.79
(1H, s, adamantyl 2-H), 5.30 (1H, d, $\underline{J}$ 8 Hz, NH), 6.84
(2H, d, $\underline{J}$ 7 Hz, Ph 2,6-H), 6.92 (1H, d, $\underline{J}$ 2 Hz, indole
2-H), 7.07-7.25 (5H, m, indole 5, 6-H, Ph 3,4,5-H),
7.34 (1H, d, $\underline{J}$ 8 Hz, ind 7-H), 7.62 (1H, d, $\underline{J}$ 8 Hz,

10   indole 4-H), 8.07 (1H, s, indole NH).

A solution of the keto diester (1.19 g, 1.89 mmol)
in ethanol (5 mL), and 6N NaOH (946 μL, 5.67 mmol) was
stirred at room temperature for 1 hour. The solvent
was removed $\underline{in\ vacuo}$ and the residue diluted with H$_2$O

15   (10 mL). This aqueous solution was acidified to pH 2
with concentrated HCl, then extracted with ethyl
acetate (3 x 50 mL). The organic extract was washed
with saturated sodium chloride solution, dried (MgSO$_4$)
and concentrated $\underline{in\ vacuo}$. The residue was taken up

20   in dioxane (30 mL) and refluxed for 18 hours. The
solvent was removed $\underline{in\ vacuo}$ and the crude material
purified by column chromatography [SiO$_2$:
toluene-acetic acid (9:1) as eluant] to give ketoacid
(10) (783 mg, 78%) as a yellow foam, m.p. 66-80°C. ^{1}H

25   NMR (300 m Hz): γ1.38-2.22 (m, 16H, adamantyl + H$_2$O),
2.55-3.25 (vbr m, 12H, CH$_2$ind, CH$_2$Ph CO, CH$_2$CH +
H$_2$O/HoD), 4.26 (m, 1H, NHC$\underline{H}$CO), 4.57 (s, 1H, adamantyl
2-H), 6.95-7.37 (m, 10H, Ph + ind 2-H, ind 5-H, ind
6H, ind 7-H + NH), 7.49 (d, $\underline{J}$ 8 Hz, 1H, ind 4-H),

30   10.58 (s, 1H, ind NH). IR (film): 3460-3200 (br,
OH), 2920 + 2856 (adamantyl) 1707 (br, ester ketone
CO, acid CO, urethane CO). Anal. C$_{32}$H$_{36}$N$_2$O$_5$ requires
C, 72.70; H, 6.86; N, 5.30%. Found C, 73.18; H, 6.98;
N, 5.05%.

EXAMPLE 5

Tricyclo[3.3.1.1^{3,7}]dec-2-yl[1-[(2-hydroxy-2-phenyl-
ethyl)amino]-3-(1H-indol-3-yl)-2-methylprop-2-yl]-
carbamate (12)

This compound was prepared by a route similar to
that used to make compound (14) (Example 6) except
that compound (11) was used. Recovered 0.42 g (43%);
m.p. 78-80°C; IR (neat) 2910, 1694 (C = O urethane)
cm^{-1}; NMR (CDCl$_3$) δ 8.1 (1H, br s, indole NH), 7.6
(1H, d, $\underline{J}$ 8 Hz, indole H-4), 7.4-7.1 (8H, m, Ph +
indole H-5, H-6, H-7), 7.0 (1H, m, indole H-2), 5.0-
4.6 (3H, m, adamantane H-2 + urethane NH + C$\underline{H}$OH), 3.5-
2.6 (6H, m, 3 x CH$_2$), 2.1-1.5 (15H, m, adamantane +
OH) 1.4 (3H, s, CH$_3$); [α]$_D$ + 18° (CHCl$_3$, 22°C, $\underline{c}$ =
0.2); FABMS (m$^+$/e)502 (m$^+$+H); anal C$_{31}$H$_{39}$N$_3$O$_3$. 0.5 H$_2$O;
requires C 72.91%, H 7.90%, N 8.23%; found: C 72.56%,
H 7.84%, N 7.95%.

EXAMPLE 6

Tricyclo[3.3.1.1^{3,7}]dec-2-yl[R-(R*,S*)]-1-[[1-(hydroxy-
methyl)-2-phenylethyl]amino]-3-(1H-indol-3-yl)-2-
methylprop-2-ylcarbamate (14)

To a solution of lithium borohydride (4 mL, 2M
solution, 8 mmol) in dry tetrahydrofuran under
nitrogen was added a solution of chlorotrimethylsilane
(1.75 g, 16.0 mmol) in dry tetrahydrofuran (5 mL). A
white ppt of lithium chloride was observed. After
2 minutes a solution of Compound (13), (1 g, 2 mmol)
in tetrahydrofuran (15 mL) was added slowly (over 3 to
4 minute period) and the reaction was stirred for
20 hours at ambient temperature. The reaction was
treated cautiously with methanol (5 mL) and the
volatiles were removed in vacuo (40°C). The residue
was purified by flash chromatography on normal phase
silica gel using hexane/ethyl acetate eluant (a

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gradient elution technique was employed, ranging from
80% hexane:20% ethyl acetate to 100% ethyl acetate).
Recovered 0.60 g starting material and 0.26 g (27%)
desired product (14) as a white foam; IR (neat) 2900,
1694 (C = O urethane)cm^{-1}; NMR (CDCl$_3$) δ 8.1 (1H, br
s, indole NH), 7.6 (1H, d, $\underline{J}$ 8 Hz, indole H-4), 7.4-
7.1 (8H, m, Ph + indole H-5, H-6, H-7), 6.9 (1H, d, $\underline{J}$
2 Hz, indole H-2), 4.9 (1H, s, urethane NH), 4.8 (1H,
s, adamantane H-2), 3.6-3.3 (2H, m, CH$_2$-OH), 3.1 (2H,
m, CH$_2$-indole), 3.0-2.6 (5H, m, 2 x CH$_2$ + 1 x CH),
2.1-1.5 (15H, m, adamantane + OH), 1.25 (3H, s, CH$_3$).

A mono-4-toluenesulphonate salt was prepared by
dissolving (14) (0.2 g, 0.4 mmol) and
4-toluenesulphonic acid monohydrate (0.074 g,
0.40 mmol) in acetone (10 mL) and subsequent removal
of solvent $\underline{in\ vacuo}$ to give a white solid;
m.p. 110-113°C. IR (neat) 2915, 1790 (C=O
urethane) cm^{-1}; $[\alpha]_D$ + 20° (CHCl$_3$, 23°C, c=1) λ FAB MS
(m$^+$/e) 516 (m$^+$ + H); anal: C$_{32}$H$_{41}$N$_3$O$_3$·C7H$_8$SO$_3$·0.5H$_2$O
Requires: C, 67.22; H, 7.23; N, 6.03; S, 4.60.
Found: C, 67.23; H, 7.26; N, 5.84; S, 4.36.

EXAMPLE 7

[R-(R*,S*)]-β-[[2-(1H-indol-3-ylmethyl)-2-[[tricyclo-
[3.3.1.1^{3,7}]dec-2-yloxycarbonyl]amino]propyl]amino]-
benzenepropanol acetate (15)

To a solution of (14) (0.05 g, 0.10 mmol) in
dichloromethane (10 mL) at ambient temperature was
added acetyl chloride (0.10 mL, 1.4 mmol) and the
reactants were stirred for 1 hour, the volatiles were
removed $\underline{in\ vacuo}$ (40°C) and the residue purified by
flash chromatography using 80% hexane : 20% ethyl
acetate as eluant. Recovered 0.024 g, (44%) of (88)
as an amorphous white solid. IR (neat) 2910, 1739 (C
= O ester), 1700 (C = O urethane)cm^{-1}; NMR (CDCl$_3$) δ

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8.2 (1H, s, indole NH), 7.6 (1H, d, $\underline{J}$ 8 Hz, indole H-
4), 7.4-7.0 (8H, m, Ph + indole H-5, H-6, H-7), 6.9
(1H, d, $\underline{J}$ 2 Hz, indole H-2), 5.1 (1H, s, urethane NH),
4.8 (1H, s, adamantane H-2), 3.9 (2H, d, $\underline{J}$ 4 Hz,
CH_2OCO), 3.1 (2H, m, CH_2-indole), 3.0-2.5 (4H, m, CH_2Ph
+ CH_2N), 2.1-1.4 (17H, m, CH_3CO + adamantane), 1.3
(3H, s, CH_3).

A mono-4-toluenesulphonate salt was prepared by
dissolving (15) (0.02 g, 0.04 mmol) and
4-toluenesulphonic acid monohydrate (0.007 g,
0.04 mmol) in acetone (5 mL) and subsequent removal of
solvent $\underline{in\ vacuo}$ to give a white solid, m.p. 98-101°C;
$[\alpha]_D$ + 32° ($CHCl_3$, 24°C, C = 0.5); FAB MS (m^+/e) 558.5
(m^+ + H); anal: $C_{34}H_{43}N_3O_4 \cdot C_7H_8SO_3 \cdot H_2O$ requires C
65.84%, H 7.14%, N 5.62%, S 4.29%. Found: C 65.48%, H
7.08%, N 5.53%, S 4.31%.

EXAMPLE 8

[R-(R*,S*)]-β-[acetyl[2-(1H-indol-3-ylmethyl)-2-
[[tricyclo[3.3.1.1^{3,7}]dec-2-yloxycarbonyl]amino]-
propyl]amino]benzene propanol acetate (15a)

To a solution of (14) (0.05 g, 0.10 mmol) in
dichloromethane (10 mL) at ambient temperature was
added triethylamine (1 mL, 7 mmol) followed by acetyl
chloride (0.1 mL, 1.4 mmol) and the reactants stirred
for 1 hour. The volatiles were removed $\underline{in\ vacuo}$ and
the residue purified by flash chromatography using
hexane:ethyl acetate as eluant. Recovered 0.043 g,
(74%) of (88a) as an amorphous solid; IR (neat) 2920,
1740 (C = O ester), 1709 (C = O urethane), 1632 (C = O
amide) cm^{-1}.

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Tricyclo[3.3.1.1^{3,7}]dec-2-yl[R-(R*,S*)]-[acetyl[1-
(hydroxymethyl)-2-phenylethyl]amino]-2-(1H-indol-3-
ylmethyl)prop-2-ylcarbamate (16)

5   To a solution of (15a) (0.03 g, 0.05 mmol) in
tetrahydrofuran (5 mL) was added a solution of lithium
hydroxide (0.1 g, 2.4 mmol) in water (5 mL) and the
reactants stirred for 15 min. The reaction was then
acidified with hydrochloric acid (2N aq) and the
products extracted with ethyl acetate (50 mL). The
10   extract was dried (magnesium sulphate) and evaporated
in vacuo (40°C). The residue was purified by flash
chromatography using hexane:ethyl acetate eluant.
Recovered 0.024 g (86%) of (89) as a white solid; m.p.
109-112°C, [α]$_D$ + 31° (22°C, CHCl$_3$, c = 0.5); IR
15   (neat) 2900, 1694 (C = O urethane), 1621 (C = O
amide)cm^{-1} ; NMR (CDCl$_3$) δ 8.1 (1H, s, indole NH), 7.5
(1H, d, J 8 Hz, indole H-4), 7.4-7.0 (8H, m, Ph +
indole H-5, H-6, H-7), 6.9 (1H, s, indole H-2), 5.3
(1H, br, urethane NH), 4.8 (1H, br, adamantane H-2),
20   4.4 (1H, s, OH), 3.9 (1H, d, J 12 Hz, one of CH$_2$OH),
3.8-3.7 (2H, m, one of CH$_2$OH + one of CH$_2$N), 3.5 (1H,
m, CH), 3.4 (1H, d, J 14 Hz, one of CH$_2$ indole), 3.3
(1H, d, J 13 Hz, one of CH$_2$N), 3.1 (2H, d, J 8 Hz,
CH$_2$Ph), 2.8 (1H, d, J 14 Hz, one of CH$_2$-indole), 2.0
25   (3H, s, CH$_3$CO), 1.9-1.4 (14H, m, adamantane), 1.1.
(3H, s, CH$_3$); anal C$_{34}$H$_{43}$N$_3$O$_4$. 0.5 H$_2$O; requires C
72.06% H 7.82% N 7.41%; found C 72.20% H 7.73% N
7.30%; FAB MS (m/e) 558 (m$^+$ + H).

EXAMPLE 9

30   Tricyclo[3.3.1.1^{3,7}]dec-2-yl (R)-[1-(1H-indol-
3-ylmethyl)-2-methyl-2-[(2-phenylethyl)amino]-
2-thioxoethyl]carbamate

      To a solution of (29) (0.1 g, 0.2 mmol) in toluene
(10 mL) was added Lawesson's reagent (0.10 g,

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0.25 mmol) and the reaction was heated to reflux for
1 hour. The reaction was allowed to cool to ambient
temperature and was purified by flash chromatography
(dichloromethane/ether eluant). Recovered 0.065 g
(63%) of 30) as a white foam, m.p. 81-85°C; IR (neat)
2916, 1703 (C=O methane), 1520 (C=S) cm^{-1}; NMR (CDCl$_3$)
γ8.1 (1H, br, indole NH), 7.8 (1H, br, this amide NH),
7.6 (1H, d, $\underline{J}$ 8 Hz, indole H-4),7.5-6.9 (9H, m, indole
H-5, H-6, H-7, H-2, + phenyl), 5.3 (1H, br, urethane
NH), 4.7 (1H, brs, adamantane H-2), 3.8 (2H, m,
CH$_2$-N), 3.6 (1H, d, $\underline{J}$ 14 Hz, one of CH$_2$-indole), 3.4
(1H, d, $\underline{J}$ 14 Hz, one of CH$_2$-indole), 2.6 (2H, m,
CH$_2$-Ph), 2.0-1.6 (14H, m, adamantane), 1.5 (3H, s,
CH$_3$); R$_f$ (30% ethyl acetate/hexane) 0.3.

EXAMPLE 10

Methyl (R)-4-[(2-hydroxy-1-phenylethyl)amino]-4-oxo-2-
butenoate (18)

To a solution of monomethyl fumarate (3.0 g,
23 mmol) in ethyl acetate (40 mL) was added
1-hydroxybenzotriazole hydrate (3.0 g, 22 mmol),
followed by $\underline{N},\underline{N}'$-dicyclohexylcarbodiimide (4.5 g,
22 mmol) and the reaction stirred at ambient
temperature for 1 hour. The solid was filtered off
and discarded. To the filtrate was added (R)-α-
phenylglycinol (3.0 g, 22 mmol) and stirring continued
for 20 minutes. The volatiles were removed in vacuo
(40°C) and the residue purified by flash
chromatography on normal phase silica gel using
hexane:ethyl acetate (1:1) as eluant. Recovered 2.5 g
(46%) of (18) as a white solid, m.p. 75-77°C; IR
(neat) 3250 (OH), 1729 (C = O ester), 1666 (C = O
amide), 1640 (C = C)cm^{-1} ; NMR (CDCl$_3$) δ 7.3-7.4 (5H,
m, Ph), 7.0 (1H, d, $\underline{J}$ 15 Hz, trans alkene), 6.8 (1H,
d, $\underline{J}$ 15 Hz, trans alkene), 6.6 (1H, br d, NH), 5.2

(1H, m, CH), 3.9 (2H, t, $\underline{J}$ 3 Hz, CH$_2$), 3.8 (3H, s, CH$_3$), 2.3 (1H, t, $\underline{J}$ 5 Hz, OH); [α]$_D$ -53° (CHCl$_3$, 24°C, $\underline{c}$ = 1); anal C$_{13}$H$_{15}$NO$_4$; requires C 62.64% H 6.07% N 5.62%; found C 62.72% H 5.92% N 5.48%.

5   <u>Tricyclo[3.3.1.1^{3,7}]dec-2-yl 3-[(1H-indol-3-yl)methyl]-
3-methyl-4,9-dioxo-7-phenyl-5,13-dioxa-2,8-diaze-
tetradec-10-enoate (19)</u>

To a solution of $\underline{N}$,$\underline{N}$'-carbonyldiimidazole (0.15 g, 0.90 mmol) in dichloromethane (40 mL) was added (23b)
10   (0.25 g, 0.63 mmol). After 20 minutes stirring at ambient temperature (18) (0.2 g, 0.8 mmol) was added and the reaction was heated to reflux for 10 hours. On cooling to ambient temperature the volatiles were removed <u>in vacuo</u> (40°C) and the residue was purified
15   by flash chromatography (hexane/ethyl acetate eluant). Recovered 0.28 g (71%) of (19) as a white solid, m.p. 96-99°C. IR (neat) 2910, 1730 (C=O ester), 1695 (C=O urethane), 1670 (C=O amide + C=C) cm^{-1}: NMR (CDCl$_3$ γ 8.3 (1H, br, indole, NH), 7.5 (1H, d, $\underline{J}$ 8 Hz, indole
20   H-4), 7.4 (1H, d, $\underline{J}$ 8 Hz, indole H-5), 7.3-6.9 (10H, m, indole H-6, H-7, H-2 + phenyl + amide NH + one of alkene CH), 5.3 (1H, br, one of CH2-O), 5.1 (1H, s, urethane NH), 5.0 (1H, br, CH), 4.8 (1H, brs, adamantane H-2), 4.1 (1H, dd, $\underline{J}$ 11 Hz, 4 Hz, one of
25   CH$_2$-O), 3.8 (3H, s, CH$_3$), 3.5 (1H, d, $\underline{J}$ 14 Hz, one of CH$_2$-indole), 3.3 (1H, d, $\underline{J}$ 14 Hz, one of CH$_2$-indole), 2.1-1.4 (18H, m, adamantane + CH$_3$): [α]$_D$ + 25° (CHCl$_3$, 24°C, C = 0.2): FAB MS (m$^+$/e) 6281 (m$^+$ + H): Anal; C$_{36}$H$_{41}$N$_3$O$_7$ requires C 68.88%; H, 6.58%; N, 6.69%; found
30   C, 68.56%; H, 6.83%; N, 6.57%.

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EXAMPLE 11

Tricyclo[3.3.1.1³,⁷]dec-2-yl 3-[(1H-indol-3-yl)methyl]-
3-methyl-4,9-dioxo-7-phenyldioxa-2,8-diazatetradec-
10-enoate (20)

5   Prepared by a route similar to that used to make
compound (19). Recovered 0.30 g (76%) of (20) as a
white solid, m.p. 104-105°C; IR (neat) 2920, 1728 (C=O
ester), 1720 (C=O) urethane), 1700 (C=C), 1670 (C=O
amide) cm⁻¹; NMR (CDCl₃; δ 8.3 (1H, br, indole NH), 7.5
10   (1H, d, J 8 Hz, indole H-4), 7.4 (1H, d, J 8 Hz,
indole H-5), 7.3-7.1 (7H, m, indole H-6, H-7 +
phenyl), 7.1-6.7 (4H, m, indole H-2 + amide NH +
alkenes), 5.3 (2H, br, urethane NH + one of CH₂-O),
4.8 (1H, br, adamantane H-2), 4.7 (1H, m, CH), 4.1
15   (1H, dd, J 11 Hz, 4 Hz, one of CH₂-O), 3.8 (3H, s,
ester, CH₃), 3.4 (1H, d, J 14 Hz, one of CH₂-indole),
3.2 (1H, d, J 14 Hz, one of CH₂-indole), 2.1-1.5 (17H,
m, adamantane + CH₃): [α]_D-36° (CHCl₃, 22°C, C=1).
FAB MS (m⁺/e) 628 (m⁺ + H): Anal; C₃₆H₄₁N₃O₇ requires
20   C, 68.88%; H, 6.58%; N, 6.69%; found: C, 68.86%; H,
6.57%; N, 6.77%.

EXAMPLE 12

Methyl (R)-4-[(2-hydroxy-1-phenylethyl)amino]-4-
oxobutanoate (21)

25   Prepared by a route similar to that used to make
compound (18) (see Example 10). Recovered 3.6 g,
(65%) of (21); m.p. 59-61°C; IR (neat) 3250 (OH), 1737
(C = O ester), 1651 (C = O amide)cm⁻¹ ; NMR (CDCl₃) δ
7.2-7.4 (5H, m, Ph), 6.4 (1H, br d, NH), 5.1 (1H, m,
30   CH), 3.7 (3H, s, CH₃), 2.8-2.5 (6H, m, 3 x CH₂), 1.7
(1H, br, OH); [α]_D -53° (CHCl₃, 22°C, c = 1); anal
C₁₃H₁₇NO₄; requires C 62.14% H 6.82% N 5.57%; found C
62.21% H 7.13% N 5.73%.

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Tricyclo[3.3.1.1^{3,7}]dec-2-yl 3-[(1H-indol-3-yl)methyl]-
3-methyl-4,9-dioxo-7-phenyl-5,13-dioxo-2,8-diazatetra-
decanoate (22)

To a solution of 1,3-dicyclohexylcarbodiimide

5   (0.3 g, 1.5 mmol) and 4-dimethylaminopyridine (0.05 g,
0.40 mmol) in dichloromethane (40 mL) was added (23)
(0.50 g, 1.3 mmol. After stirring for 20 minutes at
ambient temperature (21) (0.30 g, 12 mmol) was added
and the reaction was heated to reflux for 2 hours.

10   The volatiles were removed in vacuo (40°C and the
residue purified by flash chromatography (hexane/ethyl
acetate eluant). Recovered 0.41 g (52%) as a white
solid, m.p. 69-71°C. IR (neat 2920, 1739 (C=O ester),
1700 (C=O urethane), 1660 (C=O amide): NMR δ (CDCl

15   8.3 (1H, br, indole NH), 7.5 (1H, d, J 8 Hz, indole
H-4), 7.4-6.9 (10H, m, indole H-5, H-6, H-7, H-2 +
amide NH + phenyl), 5.3 (1H, m, CH), 5.2 (1H, brs,
urethane NH), 4.8 (2H, br, adamantane H-2 + one of
CH^2-O), 4.1 (1H, m, one of CH$_2$-O), 3.7 (3H, s, ester

20   CH$_3$), 3.4 (2H, M, CH$_2$-indole), 2.7-2.5 (4H, m, 2xCH$_2$),
2.1-1.5 (17H, m, adamantane + CH$_3$): [α]$_D$-18° (CHCl$_3$,
22°C, C=1). FAB MS (m$^+$/e), 630.0 (m$^+$ + H); Anal:
C^{36}N$_{43}$N$_3$O$_7$·0.5H$_2$O requires C, 67.69; H, 6.94; N, 6.58;
found C, 67.36; H, 6.99; N, 6.51.

25   NOTE: some small peaks at δ4.4-4.2 in the NMR
spectrum may indicate the presence of a small amount
of another isomer.

EXAMPLE 13

Tricyclo[3.3.1.1^{3,7}]dec-2-yl (R)-[2-hydroxy-1-(1H-

30   indol-3-ylmethyl)-1-methylethyl]carbamate (24)

To a solution of (23) (R=Me) (1.0 g, 2.4 mmol) in
dry THF (20 mL) at 0°C under a nitrogen atmosphere was
added a solution of lithium aluminum hydride in ether
(3 mL of a 1M solution, 3 mmol) and the reaction was

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stirred for 20 minutes. Ethyl acetate (20 mL) was
added cautiously and the resulting solution was washed
with acid (2N HCl, 2x100 mL), dried over magnesium
sulfate, and evaporated to dryness. Recovered 0.85 g

5   (91%) of (24) as a white solid, m.p. 72-74°C; IR (neat
2918, 1693 (C=O urethane) cm^{-1}; NMR (CDCl$_3$) δ 8.1 (1H,
br, indole NH), 7.6 (1H, d, J 8 Hz, indole H-4), 7.35
(1H, d, J 8 Hz, indole H-5), 7.2-7.0 (3H, m, indole
H-6, H-7, H-2), 4.85 (1H, br s, urethane NH), 4.8 (1H,

10   br, adamantane H-2), 4.0 (1H, br, OH), 3.8 (2H, m,
CH$_2$-O), 3.25 (1H, d, J 14 Hz, one of CH$_2$-indole), 3.0
(1H, d, J 14 Hz, one of CH$_2$-indole), 2.1-1.5 (14H, m,
adamantane), 1.2 (3H, s, CH$_3$); [α]$_D$ + 42° (CHCl$_3$, 22°C,
C=1); FAB MS (m/e) 383 (m$^+$ + H); Anal:

15   C$_{23}$H$_{30}$N$_2$O$_3$·0.5H$_2$O requires C, 70.56%; H, 7.98%; N,
7.15%; found: C, 7.35%; H, 7.83%; N, 6.94%.

3-(1H-indole-3-yl)-2-methyl-2-[[(tricyclo[3.3.1.1^{3,7}]-
dec-2-yloxy)carbonyl]amino]propyl (R)-benzeneacetate
(25)

20   To a solution of N,N'-carbonyldiimidazole (0.40 g,
2.5 mmol) in dichloromethane (20 mL) was added
phenylacetic acid (0.30 g, 2.2 mmol). After
10 minutes stirring at ambient temperature alcohol
(24) (0.3 g, 0.8 mmol) was added and stirring was

25   continued for 40 hours. The volatiles were removed _in_
vacuo and the residue was purified by flash
chromatography (hexane/5% ethyl acetate eluant).
Recovered 0.30 g (77%) of (25) as a white foam,
m.p. 57-60°C; IR (neat) 2917, 1722 (C=O ester), 1700

30   (C=O urethane) cm^{-1}; NMR (CDCl$_3$) δ 8.05 (1H, br, indole
NH), 7.5 (1H, d, J 8 Hz, indole H-4), 7.4-7.2 (6H, m,
indole H-5 + phenyl), 7.16 (1H, t, J 7 Hz, indole
H-6), 7.07 (1H, t, J 7 Hz, indole H-7), 6.9 (1H, d, J
2 Hz, indole H-2), 4.8 (1H, br, adamantane H-2), 4.6

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(1H, br, urethane NH), 4.3 (1H, d, $\underline{J}$ 11 Hz, one of
CH$_2$-O), 4.2 (1H, d, $\underline{J}$ 11H, one of CH$_2$-O), 3.7 (2H, s,
CH$_2$-Ph, 3.2 (1H, d, $\underline{J}$ 14 Hz, one of CH$_2$-indole), 3.0
(1H, d, $\underline{J}$ 14 Hz, one of CH$_2$-indole), 2.1-1.4 (14H, m,

5   adamantane), 1.2 (3H, s, CH$_3$); [α]^D+13° (CHCl$_3$, 22°C,
C=0.5); FAB MS 501 (m$^+$ + H). Anal: C$_{31}$H$_{36}$N$_2$O$_4$
requires C, 74.37%; H, 7.25%; N, 5.60%; found: C,
74.20%; H, 7.32%; N, 5.52%.

Tricyclo[3.3.1.1^{3,7}]dec-2-yl (R)-[1-formyl-2-(1H-indol-
10   3-ylmethyl)-1-methylethyl]carbamate (26)
        To a solution of (24) (0.03 g, 0.08 mmol) in
dichloromethane (40 mL) at ambient temperature under
argon was added N-methylmorpholine-N-oxide (0.1 g,
0.9 mmol), molecular sieves (4A activated powder,

15   0.5 g), and tetra-n-propylammonium perruthenate
(0.01 g, 0.03 mmol). After stirring for 30 minutes
the volatiles were removed $\underline{in\ vacuo}$ (40°C). The
residue was taken up in ethyl acetate and purified by
flash chromatography (hexane/5% ethyl acetate eluant).

20   Recovered 0.2 g (67%) of (24) as a white solid, m.p.
178-179°C; IR (neat) 2900, 1732 (C=O aldehyde), 1692
(C=O urethane) cm^{-1}; NMR (CDCl$_3$), δ 9.6 (1H, s, CHO),
8.1 (1H, br s, indole NH), 7.6-6.9 (5H, m, indole),
5.2 (1H, br, urethane NH), 4.8 (1H, s, adamantane

25   H-2), 3.3 (2H, br, CH$_2$-indole), 2.1-1.3 (17H, m,
adamantane + CH$_3$); [α]^D + 22D (CHCl$_3$, 22°C, C=1); FAB
MS (m$^+$/e) 381 (m$^+$ + H). Anal: C$_{23}$H$_{28}$N$_2$O$_3$ requires C,
72.61%; H, 7.42%; N, 7.36%; found: C, 72.31%; H,
7.46%; N, 7.31%.

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EXAMPLE 14

Tricyclo[3.3.1³,⁷]dec-2-yl [R-(Z)]-[1-(1H-indol-3-yl-
methyl)-1-methyl-5-phenyl-2-pentenyl]carbamate (27)

A mixture of triphenylphosphine (0.35 g, 1.3 mmol)
and 1-bromo-3-phenylpropane (0.27 g, 1.3 mmol) was
heated to 110°C, at which point the molten reactants
solidified. On cooling to ambient temperature and
trituration with hexane a white solid was recovered
(0.4 g, 65%). This was added to a suspension of
sodium hydride (50 mg of 50% in oil dispersion,
1 mmol) in toluene (40 mL) and the reaction was
refluxed for 20 minutes. Aldehyde (0.2 g, 0.5 mmol)
was added and heating continued 1 hour. The volatiles
were removed _in vacuo_ and the residue purified by
flash chromatography (hexane/10% ethyl acetate
eluant). Recovered 0.20 g (79%) of (27) as a white
solid, m.p. 49-52°C; IR (neat) 2904, 1696 (C=O
urethane), 1683 (C=C) cm^{-1}; NMR (CDCl$_3$): δ 8.3 (1H, s,
indole NH), 7.6 (1H, d, _J_ 8 Hz, indole H-4), 7.3-7.0
(8H, m, indole H-5, H-6, H-7 + phenyl), 6.9 (1H, s,
indole H-2), 5.6 91H, d, _J_ 12hz, CH by α-centre), 5.4
(1H, dt, _J_ 5, 12 Hz, CH-CH$_2$), 4.8 (2H, m, urethane NH
+ adamantane H-2), 3.3 (1H, d, _J_ 14 Hz), one of
CH$_2$-indole), 3.1 (1H, d, _J_ 14 Hz, one of CH$_2$-indole),
2.6-2.4 (4H, m, 2xCH$_2$), 2.1-1.4 (14H, m, adamantane),
1.4 (3H, s, CH$_3$).

EXAMPLE 15

Tricyclo[3.3.1.1³,⁷]dec-2-yl[2-hydroxy-1-(1H-indol-
3-ylmethyl)-1-methyl-5-phenylpentyl]carbamate (28)

To a stirred mixture of magnesium metal (0.5 g,
21 mmol) and dry ether (20 mL) at 0°C under a nitrogen
atmosphere was added 1-bromo-3-phenylpropane (0.20 mL,
0.26 g, 1.3 mmol) and one crystal of iodine. After
20 minutes the reaction mixture became colorless, so

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the solution was removed by syringe and added to a
solution of (26) (0.30 g, 0.8 mmol) in dry ether at
0°C under a nitrogen atmosphere. After 20 minutes the
reaction was allowed to warm to ambient temperature

5   and was quenched in dilute hydrochloric acid (2N,
50 mL). The products were extracted with ethyl
acetate (50 mL), dried over magnesium sulfate, and
evaporated _in vacuo_. The residue was purified by
flash chromatography (hexane:ethyl acetate eluant);

10   recovered 0.31 g (79%) of (28) as an oil which appears
to be a 1:1 mixture of the possible diastereomers.
Further chromatography gave a single diastereoisomer:
IR (neat) 2908, 1690 (C=O urethane): NMR (CDCl$_3$)
δ 8.1 (1H, br, indole NH), 7.6 (1H, d, $\underline{J}$ 8 Hz, indole

15   H-4), 7.4-6.9 (9H, n, indole H-5, H-6, H-7, H-2 +
phenyl), 4.8 (1H, br, adamantane H-2), 4.7 (1H, br s,
urethane NH), 3.6 (1H, m, CH-OH), 3.5 (1H, d, $\underline{J}$ 14 Hz,
one of CH$_2$-indole), 3.1 (1H, d, $\underline{J}$ 14 Hz, one of
CH$_2$-indole), 2.7 (2H, m, CH$_2$-Ph), 2.1-1.3 (19H, m,

20   adamantane + 2xCH$_2$ + OH), 1.1 (3H, s, CH$_3$).

EXAMPLE 16
Tricyclo[3.3.1.1^{3,7}]dec-2-ylR-(R*,S*)]-[1-[4,5-
dihydro-4-(phenylmethyl)-2-thiazolyl]-2-(1H-indol-
3-yl)-1-methylethyl]carbamate (17)

25   To a solution of (13) (0.1 g, 0.2 mmol) in toluene
(10 mL) was added Lawesson's reagent (0.10 g,
0.25 mmol) and the reaction was heated to reflux for
1 hour. The reaction mixture was allowed to cool to
ambient temperature and was purified by flash

30   chromatography (dichloromethane/ether eluant).
Obtained 0.07 g (70%) of the product; IR (neat) 2910,
1697 (C=O urethane), 1620 (C=N) cm^{-1}: NMR (CDCl$_3$ δ 8.1
(1H, br, indole NH), 7.7 (1H, d, $\underline{J}$ 8 Hz, indole H-4),
7.4-6.9 (9H, m, indole H-5, H-6, H-7, H-2 + phenyl),

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5.8 (1H, br, urethane NH), 4.9 (1H, br, adamantane
H-2), 4.6 (1H, m, CH), 3.7 (1H, m, one of CH_2-S), 2.9
(1H, m, one of CH_2-S), 2.8 (1H, br, one of CH_2-Ph),
2.2 (1H, br, one of CH_2-Ph), 2.1-1.4 (14H, m,
adamantane), 1.3 (3H, s, CH_3); FAB MS (m^+/e) 529 (m^+ _
H), 47%), 398 (m^+-(indole-CH_2), 44%), 130 (indole-CH_2),
100%): R_f (30% ethyl acetate/hexane), 0.85.

EXAMPLE 17

Phenylmethyl (R)-ß-methyl-ß-[[(tricyclo[3.3.1.1^{3,7}]dec-
2-yloxy)carbonyl]amino]-1H-indole-3-butanoate

Step 1

A solution of N-methyl morpholine (253 mg,
2.50 mmol) and 2-Adoc-αMe-R-TrpOH (23b) (990 mg,
2.50 mmol) in anhydrous THF (20 mL) was cooled to 0°C
and treated with a solution of i-butylchloroformate
(360 mg, 2.5 mmol) in anhydrous THF (10 mL) dropwise
over 10 mm. This was stirred at 0°C for a further
20 minutes and filtered. A solution of diazomethane
(6 mmol) in Et_2O was added to the filtrate and left at
0°C for 4 hours, then allowed to warm slowly to room
temperature over 12 hours. Excess diazomethane was
quenched with acetic acid and the solvents removed <u>in</u>
<u>vacuo</u>. The residue was chromatographed using 25%
EtOAc in n-hexane to give the diazoketone (300 mg,
29%); IR (film) 3400-3200, 2913, 2854, 2106, 1693, and
1353 cm^{-1}; NMR (CDCl$_3$) δ 1.49 (3H, s), 1.50-1.60 (2H,
m,), 1.70-2.05 (12H, m), 3.30-3.40 (2H, br s), 4.86
(1H, br s), 5.20-5.40 (1H, br s), 5.56 (1H, s), 6.95
(1H, d, J 2 Hz), 7.08 (1H, t, J 7 Hz), 7.16 (1H, t, J
7 Hz), 7.33 91H, d, J 8 Hz), 7.55 (1H, d, J 8 Hz),
8.50 (1H, s).

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Step 2

A solution of the diazoketone (Scheme 5, No. 31)
(1.04 g, 2.50 mmol) in benzyl alcohol (10 mL) was
treated with a solution of silver benzoate (4 mL,
17 mmol) in triethylamine (5 mL) portionwise, and left
to stir for 1 hour. EtOAc (30 mL) was then added and
this solution treated with activated charcoal and
filtered through a filter and the solvent was removed
in vacuo and the residue chromatographed using 30%
EtOAc in n-Hexane as eluant to give the benzyl ester
(44.0 mg, 35%); IR (film) 3500-3200, 2907, 2855, 1720
and 1698 cm^{-1}; NMR (CDCl$_3$) δ 1.37 (3H, s), 1.50-1.55
(2H, m), 1.65-1.85 (8H, m), 1.90-2.05 (4h, m), 2.67
(1H, d, J 14.5 Hz, 2.97 (1H, d, J 14.5 Hz), 3.22 91H,
d, J 14 Hz), 3.29 (1H, d, J 14 Hz), 4.68 (1H, s), 4.82
(1H, s), 5.09 (2H, s), 6.95 (1H, d, J 2 Hz), 7.06 (1H,
dt, J 7.5 and 1 Hz), 7.15 (1H, dt, J 7.5 and 1 Hz),
7.25-7.35 (6H, m), 7.57 (1H, d, J 8 Hz), 8.28 (1H, s).

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EXAMPLE 18

Tricyclo[3.3.1.1^{3,7}]dec-2-yl [R-(R*,S*)][3-[[1-
(hydroxymethyl)-2-phenylethyl]amino]-1-(1H-indol-3-
ylmethyl]-1-methyl-3-oxopropyl]carbamic acid
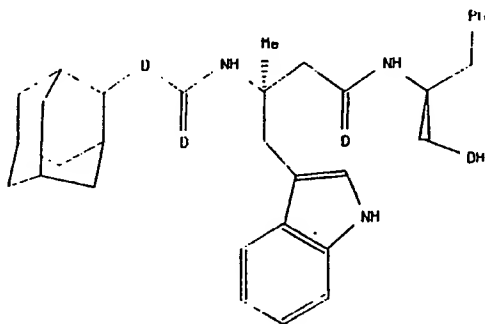
Step 1

A solution of benzyl ester (Example 17, Scheme 5
No. 32) (440 mg, 0.88 mmol) in absolute EtOH (100 mL)
was treated with Pd/C (50 mg, Ca 10% w/w) and put
under an atmosphere of hydrogen at 50 psi and 30°C
with agitation for 16 hours. The reaction mixture was
filtered through a filter aid and the filtrate
evaporated to dryness _in vacuo_. The residue was
chromatographed over reverse phase silica using 25%
H_2O in MeOH as eluant to give the acid (180 mg 50%),
m.p. 91-99°C (MeOH/H_2O); $[\alpha]^D$ + 20.0° (C=1, MeOH); IR
(film) 3500-3300, 2912, 285?, 1704 cm^{-1}; NMR (CDCl$_3$)
δ 1.41 (3H, s), 1.53 (1H, s), 1.57 (1H, s), 1.70-1.85
(9H, m), 1.95-2.10 (4H, m), 2.69 (1H, d, _J_ 14.5 Hz),
3.05 (1H, d, _J_ 14.5 Hz), 3.21 (1H, d, _J_ 14.5 Hz), 3.32
(1H, d, _J_ 14.5 Hz), 4.86 (1H, s), 5.10-5.30 (1H, br
s), 7.04 (1H, d, _J_ 2hz), 7.07-7.20 (2H, m), 7.35 (1H,
d, _J_ 8 Hz), 7.60 (1H, d, _J_ 8 Hz), 8.16 (1H, s).

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Step 2

      A solution of the carboxylic acid (Step 1,
Scheme 5, No. 33) (160 mg, 0.39 mmol) and
pentafluorophenol (72 mg, 0.39 mmol) in EtOAc (20 mL)

5   was cooled to 0°C and treated with a solution of
N,N'-dicyclohexylcarbodiimide (80 mg, 0.39 mmol) in
EtOAc (5 mL) and left stirring at 0°C for 18 hours.
After this time it was filtered and S-phenyl alaninol
added (121 mg, 0.8 mmol), and the mixture left at room

10   temperature for 24 hours. The solvent was then
removed in vacuo and the residue chromatographed using
30% EtOAc in n-Hexane as eluant to give the product as
a white solid (140 mg, 66%); IR (film) 3500-3200,
2909, 2855, 1694, 1651, and 1570 cm^{-1}; NMR (CDCl$_3$)

15   δ 1.27 (3H, s), 1.51 (1H, s), 1.55 (1H, s), 1.70-2.05
(12H, m), 2.46 (1H, d, J 13.5 Hz), 2.75-2.81 (2H, m),
2.87 (1H, d, J 13.5 Hz), 2.90-3.05 (1H, br), 3.08 (1H,
d, J 14 Hz), 3.28 (1H, d, J 14 Hz), 3.50 (1H, dd, J 11
and 5 Hz), 3.61 (1H, dd, J 11 and 3.5 Hz), 4.10-4.20

20   (1H, m), 4.81 (1H, s), 5.14 (1H, s), 6.26 (1H, d, J
8 Hz), 6.99 (1H, d, J 2 Hz), 7.08 (1H, t, J 7 Hz),
7.10-7.30 (6H, m), 7.33 (1H, d, J 8 Hz), 7.58 (1H, d,
J 8 Hz), 8.32 (1H, s).

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EXAMPLE 19

<u>Carbamic acid, [1-(1H-indol-3-ylmethyl)-1-methyl-2-
[(1-oxo-4-phenylbutyl)amino]ethyl]-, tricyclo-
[3.3.1.1^{3,7}]dec-2-yl ester (R)-</u>
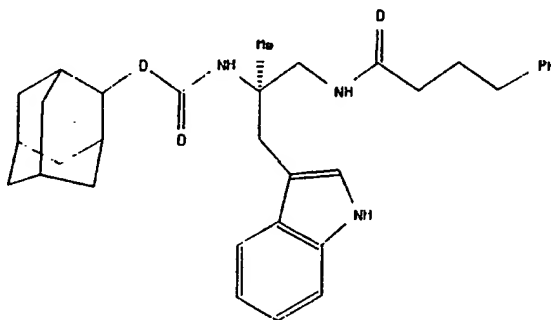
5　　　This was prepared in the same manner as described
in Example 21. Scheme 5 No. 37d, m.p. 70-75°C (foam);
$[\alpha]^D$-9.2 (C=1, MeOH); IR (film) 3400-3100, 2908, 2853,
694, 1645, and 1526 cm^{-1}; NMR (CDCl$_3$) δ 1.24 (3H, s),
1.50-2.10 (16H, m), 2.20 (2H, t, <u>J</u> 7 Hz), 2.64 (2H, t,
10　　<u>J</u> 7 Hz), 2.98 (1H, d, <u>J</u> 14.5 Hz), 3.25 (1H, d, <u>J</u>
14.5 Hz), 3.55 (1H, dd, <u>J</u> 14 and 6 Hz), 3.70 (1H, dd,
<u>J</u> 14 and 6 Hz), 4.81 (1H, s), 4.94 (1H, s), 6.50-6.60
(1H, br s), 7.00 (1H, d, <u>J</u> 2 Hz), 7.05-7.30 (7H, m),
7.35 (1H, d, <u>J</u> 8 Hz), 7.57 (1H, d, <u>J</u> 8 Hz), 8.17 (1H,
15　　s); Anal. C$_{33}$H$_{41}$N$_3$O$_3$, C, H, N.

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EXAMPLE 20

Carbamic acid, [2-(benzoylamino)-1-(1H-indol-3-ylmethyl)-1-methylethyl]-, tricyclo[3.3.1.1³,⁷]dec-2-yl ester, (R)-
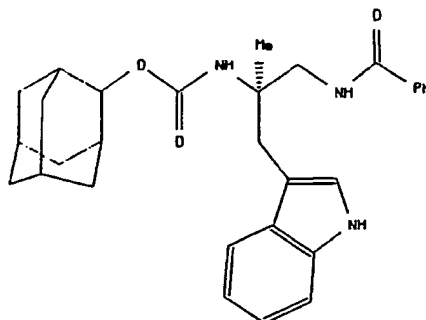
5   This was prepared in the same manner as described in Example 21. Scheme 5 No. 37a, m.p. 220.0-220.1°C (MeOH); $[\alpha]_D$ + 24°C (C=0.25, MeOH); IR (film) 3500-3200-2907, 2855, 1695, 1646, and 1533 cm^{-1}; NMR (CDCl$_3$) δ 1.30 (3H, s), 1.50-1.60 (2H, m), 1.70-2.10
10   (12H, m), 3.07 (1H, d, J 14.5 Hz), 3.31 (1H, d, J 14.5 Hz), 3.76 (1H, dd, J 14 and 6 Hz), 3.89 (1H, dd, J 14 and 6 Hz), 4.84 (1H, s), 5.03 (1H, s), 7.01 (1H, d, 2 Hz), 7.05-7.20 (2H, m), 7.35-7.50 (4H, m), 7.60 (1H, d, J 8H, 7.77 (2H, d, J 7 Hz), 7.60-7.90 (1H,
15   br), 8.39 (1H, s); FAB MS m/e 486.3 (34), 355.3 (63), 290.3 (29), 177.2 (37), 154.1 (100); Anal. C$_{30}$H$_{35}$N$_3$O$_3$; C, H, N.

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EXAMPLE 21

Carbamic acid, [1-(1H-indol-3-ylmethyl)-1-methyl-2-
[(1-oxo-3-phenylpropyl)amino]ethyl-, tricyclo-
[3.3.1.1^{3,7}]dec-2-yl ester, (R)-
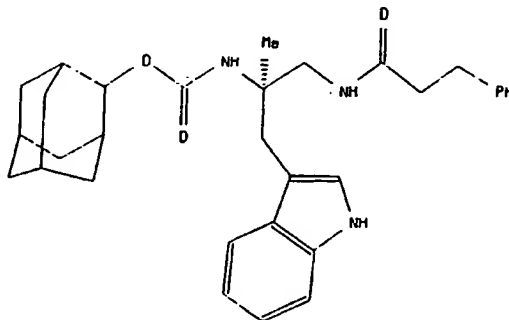
5   Step 1

Carbamic acid, [2-amino-1-(1H-indol-3-ylmethyl)-1-
methyl-2-oxoethyl)-, tricyclo[3.3.1.1^{3,7}]dec-2-yl
ester, (R)- AdOC-α-Me)DTrp-NH$_2$ (See Scheme 5, No. 35
2-Adoc-α-Me-R-Trp NH$_2$)
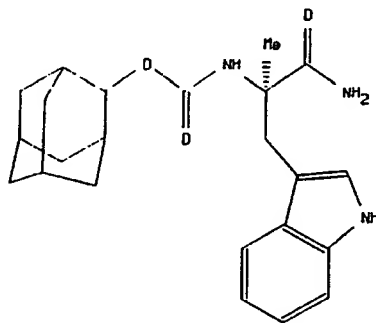
10   2-Adoc-α-Me-R-TrpOH (23b) (9.5 g, 24 mmol) as a
solution in EtOAc (150 mL) was treated with
pentafluorophenol (4.4 g, 24 mmol) and cooled to 0°C.
A solution of N,N'-dicyclohexylcarbodiimide (5.15 g,
25 mmol) in EtOAc (20 mL) was added dropwise and the
15   resultant mixture allowed to stir 6 hours, then left a
further 12 hours at 4°C. This was then filtered and
the filtrate evaporated to dryness in vacuo. The

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residue was redissolved in THF (100 mL) and ammonia
gas bubbled through at 0°C for 1 hour. The solvent
was removed _in vacuo_ and the residue chromatographed
over reverse phase silica using 30% H_2O in MeOH as
5   eluant to give the amide (35, Scheme 5) (9.2 g, 97%)
as white crystals, m.p. 136-149°C (MeOH); $[\alpha]_D$ + 42.1
(C=1), MeOH); ·IR (film) 3351, 2906, 2855, 1675, and
1588 cm^{-1}; NMR ($CDCl_3$) δ 1.50-1.60 (2H, m), 1.58 (3H,
s), 1.70-2.05 (12H, m), 3.33 (1H, d, $\underline{J}$ 14.5 Hz), 3.51
10   (1H, d, $\underline{J}$ 14.5 Hz), 4.86 (1H, s), 5.24 (1H, s),
5.40-5.55 (1H, br), 6.20-6.35 (1h, br), 7.04 (1H, d, $\underline{J}$
2 Hz), 7.08-7.21 (2H, m), 7.36 (1H, d, $\underline{J}$ 8 Hz), 7.63
(1H, d, $\underline{J}$ 8 Hz), 8.24 (1H, s); MS (FAB) m/e 396 (100);
Anal. $C_{23}H_{29}N_3O_3$; C, H, N.

15   Step 2 (See Scheme 5, No. 36)
        Trimethylsilylchloride (4.34 g, 40 mmol) was added
dropwise to a solution of $LiBH_4$ (11 mL of a 2M
solution, 22 mmol) in THF under an atmosphere of
nitrogen. A solution of 2-AdocαMe-$\underline{R}$-TrpNH$_2$ (Scheme 5,
20   N°35) from the previous step (3.95 g, 10.0 mmol) in
anhydrous THF (20 mL) was added dropwise over 20 mm
and the reaction mixture stirred 10 minutes at room
temperature, then at gentle reflux for 3 hours. This
was then cooled to 0°C and MeOH (16.5 mL) added with
25   caution. All solvents were then removed _in vacuo_ and
the residue chromatographed over reverse phase silica
using 30% H_2O in MeOH as eluant to give 1.25 g (32%)
of starting amide and 1.29 g (34%) of the product
amine, m.p. 138-144°C (MeOH); $[\alpha]^D$ + 51.6° (C=1,
30   MeOH); IR (film) 2912, 2854 and 1690 cm^{-1}; NMR ($CDCl_3$)
δ 1.32 (3H, s), 1.40-1.55 (2H, m), 1.65-2.05 (12H, m),
3.04 (1H, d, $\underline{J}$ 14 Hz), 3.20-3.30 (2H, m), 3.40-3.50
(1H, m), 4.78 (1H, s), 5.10-5.30 (1H, br s), 7.00-7.20
(3H, m), 7.34 (1H, d, $\underline{J}$ 8 Hz), 7.52 (1H, d, $\underline{J}$ 8 Hz),

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8.56 (1H, s), 8.67 (2H, br s); FAB MS m/e 382.3 (100).

Step 3 (See Scheme 5, No. 37c)

A solution of 3-phenylpropionic acid (75 mg,
0.5 mmol) in EtOAc (5 mL) was treated with
5   pentafluorophenol (92 mg, 0.5 mmol) and cooled to 0°C.
A solution of N,N'-dicyclohexylcarbodiimide (103 mg,
0.5 mmol) in EtOAc (2 mL) was added and the mixture
left 12 hours at 4°C. This mixture was then filtered
and solid amine (from Step 2, Scheme 5 N°36) (198 mg,
10   0.5 mmol) added, and left at room temperature for
24 hours. The reaction mixture was washed with 1M
citric acid solution (2 x 10 mL), NaHCO$_3$ (2 x 10 mL of
a 1M solution), and H$_2$O (2 x 10 mL) and the organic
phase dried over MgSO$_4$. The solvent was then removed
15   in vacuo and the residue chromatographed over silica
gel using 2% MeOH in CH$_2$Cl$_2$ eluant to give the product
(230 mg, 90%) as white crystals, m.p. 171-175°C
(MeOH); [α]°$_D$-12.3° (C=0.56, MeOH); IR (KBr)
3400-3100, 2906, 2854, 1694, 1649, an 1528 cm^{-1}; NMR
20   (CDCl$_3$) δ 1.13 (3H, s), 1.50-2.10 (14H, m), 2.50 (2H,
t, J 7 Hz), 2.90 (1H, d, J 14 and 6 Hz), 3.65 (1H, dd,
J 14 and 6 Hz), 4.81 (1H, s), 4.88 (1H, s), 6.40-6.60
(1H, br), 6.96 (1H, d, J 3 Hz), 7.05-7.30 (7H, m),
7.35 (1H, d, J 8 Hz), 7.53 (1H, d, J 8 Hz), 8.15 (1H,
25   s); FAB MS m/e 514.4 (8), 383.3 (32), 205.2 (32),
170.2 (47), 135.2 (100); Anal. C$_{32}$H$_{39}$N$_3$O$_3$; C, H, N.

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EXAMPLE 22

Carbamic acid, [1-(1H-indol-3-ylmethyl)-1-methyl-2-
[(2-phenylacetyl)amino]ethyl]-, tricyclo[3.3.1.1³,⁷]-
dec-2-yl ester, (R)-
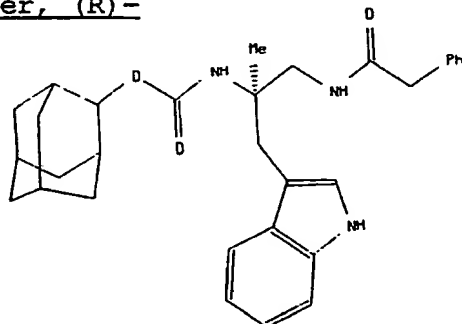
5   This was prepared in the same manner as described
in Example 21 (see Scheme 5, No. 37b), m.p.
176.5-180°C (MeOH); [α]$_D$-1.6° (C=O 56, MeOH); IR
(film) 3400-3100, 2911, 2854, 1694, 1656, and 1520 cm⁻
¹; NMR (CDCl₃) δ 1.16 (3H, s), 1.50-2.10 (14H, m),
10   2.90 (1H, d, J 14 Hz), 3.16 (1H, d, J 14 Hz), 3.50
(1H, dd, J 14 and 6 Hz), 3.57 (2H, s), 3.65 (1H, dd, J
14 and 6 Hz), 4.73 (1H, s), 4.80 (1H, s), 6.30-6.40
(1H, brs), 6.94 (1H, d, J 2 Hz), 7.07 (1H, t, J 8 Hz),
7.16 (1H, t, J 8 Hz), 7.25-7.40 (6H, m), 7.48 (1H, d,
15   J 8 Hz), 8.11 (1H, s); FAB MS m/e 500.5 (100), 369.3
(87); Anal. C₃₁H₃₇N₃O₃; C, H, N.

EXAMPLE 23

Carbamic acid, [2-[[3-[[1-(hydroxymethyl)-2-phenyl-
ethyl]amino]-3-oxopropyl]amino]-1-(1H-indol-
20   3-ylmethyl)-1-methyl-2-oxoethyl]-, tricyclo-
[3.3.1.1³,⁷]dec-2-yl ester, [R-(R*,S*)]-

       The acid as prepared in Example 30, Step 2
(1.17 g, 2.80 mmol) and pentafluorophenol (461 mg,
2.5 mmol) as a solution in EtOAc (50 mL) was treated
25   with dicyclohexyl carbodiimide (542 mg, 2.60 mmol) and
left at 0°C for 18 hours. This was filtered and the
filtrate treated with s-phenylalaninol (454 mg,

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3.00 mmol) and the reaction mixture left stirring
18 hours at room temperature. This was then
concentrated _in vacuo_ and the residue chromatographed
over reverse phase silica using 75% MeOH in H_2O as
eluant to give the product as a white, noncrystalline
solid (1.17 g, 78%); m.p. 94-98°C; $[\alpha]_{D20}$ + 14.7°
(c=1), MeOH); IR (film) 3306, 2904, 2854, 1693, and
1651 cm^{-1}; NMR (DMSO-d_6) δ 1.29 (3H, s), 1.60-2.00
(14H, m), 2.05-2.25 (2H, m), 2.62 (1H, dd, _J_ 14 and
8 Hz), 2.83 (1H, dd, _J_ 14 and 6 Hz), 3.10-3.40 (5H,
m), 3.85-3.95 (1H, m), 4.70-4.80 (2H, m), 6.70 (1H, br
s), 6.90-7.35 (9H, m), 7.44 (1H, d, _J_ 8 Hz), 7.70 (1H,
d, _J_ 8 Hz), 7.75 (1H, br s), 10.85 (1H, s); FAB MS m/e
601 (m+1), 100); Anal. $C_{35}H_{44}N_4O_5 \cdot 0.25H_2O$; C, H, N.

EXAMPLE 24

Carbamic acid, [1-(1H-indol-3-ylmethyl)-2-[[3-[[1-
hydroxymethyl)-2-phenylethyl]amino]-3-oxopropyl]-
amino]-1-methyl-2-oxoethyl]-, tricyclo[3.3.1.1^{3,7}]dec-
2-ylester, [S-(R*,R*)]-
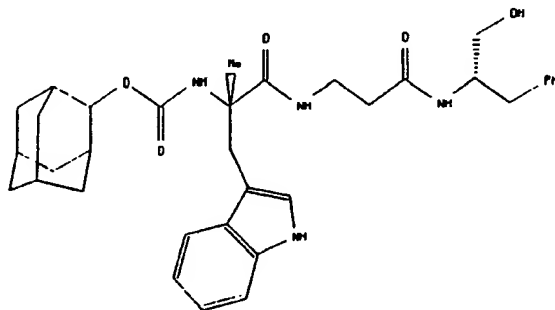
This was prepared in the same manner as described
in Example 23 (see Scheme 6, No. 44), m.p. 95-97°C
(MeOH/H_2O); $[\alpha]_D^{20}$-31.3° (c=1), MeOH); IR (film) 3314,
2910, 2856, 1696, and 1651 cm^{-1}; NMR (CDCl$_3$) δ 1.53
(5H, s), 1.70-2.05 (12H, m), 2.10-2.30 (2H, M), 2.79
(2H, d, _J_ 7 Hz), 3.25 (1H, d, _J_ 14.5 Hz), 3.35 (1H, d,
_J_ 14.5 Hz), 3.30-3.55 (3H, m), 3.65-3.70 (1H, m),

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4.10-4.20 (1H, m), 4.79 (1H, s), 5.26 (1H, s), 6.20-
6.35 (1H, br s), 6.69 (1H, t, _J_ Hz), 6.97 (1H, d, _J_
2 Hz), 7.06-7.29 (7H, m), 7.34 (1H, d, _J_ 8 Hz), 7.57
(1H, d, _J_ 8 Hz), 8.49 (1H, s); FAB MS m/e 601 (100);
Anal. $C_{35}H_{44}N_4O_5\cdot0.25H_2O$; C, H, N. MS FAB m/e 614 (m+1)
and 217 (100); Anal. $C_{35}H_{43}N_5O_5\cdot0.5H_2O$; C, H, N.

EXAMPLE 25

D-Phenylalanamide, α-methyl-N-[(tricyclo[3.3.1.1^{3,7}]-
dec-2-yloxy)carbonyl]-D-tryptophyl-ß-alanyl-
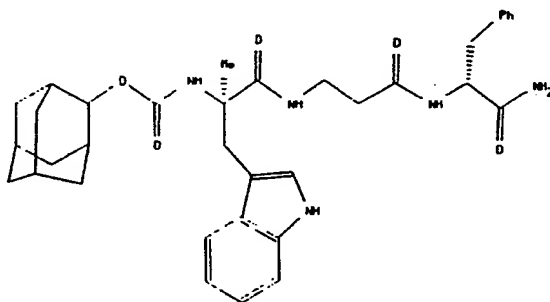
This was prepared using a method similar to
Example 26. The acid from Example 30, Step 2 (117 mg,
0.25 mmol) and pentafluorophenol (46 mg, 0.25 mmol) as
a solution in EtOAc (10 mL) was treated with
dicyclohexylcarbodiimide (52 mg, 25 mmol) and left
stirring at room temperature for 2 hours before being
filtered. S-Phenylalaninamide (50 mg, 0.3 mmol) was
then added and the mixture left stirring at room
temperature for 72 hours. The reaction mixture was
then washed with 1M HCl (10 mL), H_2O (10 mL), 1M NaOH
(10 mL), and H_2O (10 mL). The organic phase was dried
over $MgSO_4$ and concentrated _in vacuo_. The residue was
chromatographed over reverse phase silica gel using
75% MeOH in H_2O as eluant to give the product as a
white noncrystalline solid (130 mg, 85%); m.p.

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113-118°C; $[\alpha]_D^{20}$ + 27.5° (C=0.5, MeOH); IR (film)
3311, 3055, 2908, 1700, and 1659 cm^{-1}; NMR (CDCl$_3$)
δ 1.49 (2H, s), 1.52 (3H, s), 1.60-2.05 (12H, m), 2.19
(2H, t, J 6 Hz), 3.01 (1H, dd, J 7.5 and 14 Hz), 3.08
(1H, dd, J 7.5 and 14 Hz), 3.27 (1H, d, J 14.5 Hz),
3.42 (1H, d, J 14.5 Hz), 3.35-3.50 (2H, m), 4.59 (1H,
dd, J 15 and 7 Hz), 4.80 (1H, s), 5.29 (1H, s), 5.47
(1H, s), 6.20 (1H, s), 6.50 (1H, d, J 7 Hz), 6.76 (1H,
t, J 6 Hz), 6.96 (1H, d, J 2 Hz), 7.05-7.35 (7H, m),
7.34 (1H, d, J 8 Hz), 7.57 (1H, d, J 8 Hz), 8.36 (1H,
s).

EXAMPLE 26
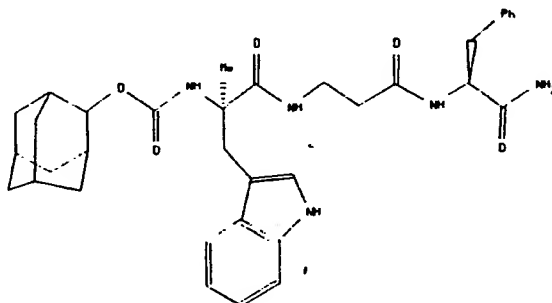
L-Phenylalaninamide, α-methyl-N-[(tricyclo[3.3.1.1^{3,7}]-
dec-2-yloxy)carbonyl]-D-tryptophyl-ß-alanyl-

m.p. 112-118°C (MeOH/H$_2$O); $[\alpha]_D^{20}$ + 16.3° (c=1, MeOH);
IR (film) 3309, 2907, 2855, 1690, 1652 cm^{-1}; NMR
(CDCl$_3$) δ 1.50-2.05 (17H, m), 2.10-2.20 (2H, m), 2.98
(1H, dd, J 14 and 8 Hz), 3.09 (1H, dd, J 14 and 7 Hz),
3.24 (1H, d, J 14.5 Hz), 3.35 (1H, d, J 14.5 Hz),
3.25-3.55 (2H, m), 4.58 (1H, dd, J 15 and 7.5 Hz),
4.78 (1H, s), 5.28 (1H, s), 5.48 (1H, s), 6.27 (1H, br
s), 6.54 (1H, br s), 6.75 (1H, m), 6.99 (1H, d, J
2 Hz), 7.05-7.30 (7H, m), 7.34 (1H, d, J 8 Hz), 7.58

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(1H, d, $\underline{J}$ 8 Hz), 8.41 (1H, s); FAB MS m/e 614.3 (100);
Anal. $C_{35}H_{43}N_5O_5$0.75H_2O; C, H, N.

EXAMPLE 27
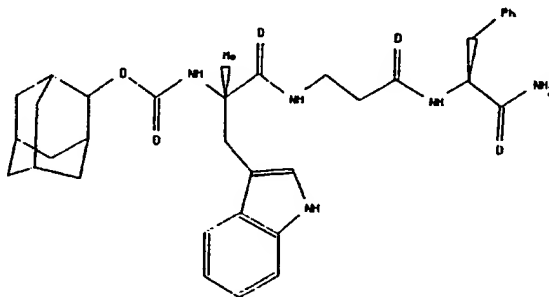
L-Phenylalaninamide, α-methyl-N-[(tricyclo[3.3.1.1^{3,7}]-
dec-2-yloxy)carbonyl]-L-tryptophyl-ß-alanyl-

m.p. 114-119°C (MeOH/H_2O); $[\alpha]_D^{20}$-15.2° (c=0.5, MeOH);
IR (film) 3323, 2909, 2855, 1700-1640 cm^{-1}; NMR (CDCl$_3$)
δ 1.50 (2H, s), 1.54 (3H, s), 1165-2.00 (12H, m),
2.10-2.20 (2H, br s), 2.95 (1H, dd, $\underline{J}$ 14 and 8 Hz),
3.10 (1H, dd, $\underline{J}$ 14 and 6 Hz), 3.23 (1H, d, $\underline{J}$ 14 Hz),
3.32 (1H, d, $\underline{J}$ 14H), 3.20-3.30 (1H, m), 3.40-3.50 (1H,
m), 4.55 (0.5H, 0, $\underline{J}$ 8 Hz), 4.60 (0.5H, d, $\underline{J}$ 8 Hz),
4.78 (1H, s), 5.35 (1H, s), 5.68 (1H, s), 6.41 (1H,
s), 6.65-6.85 (1H, m), 6.82 (1H, t, $\underline{J}$ 6 Hz), 6.97 (1H,
d, $\underline{J}$ 2 Hz), 7.05-7.30 (7H, m), 7.33 (1H, d, $\underline{J}$ 8 Hz),
7.57 (1H, d, $\underline{J}$ 8 Hz), 8.55 (1H, s); FAB MS m/e 614.3
(50.7), 236.1 (100); Anal. $C_{35}H_{43}N_5O_5$·0.5H_2O; C, H, N.

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EXAMPLE 28

<u>D-Phenylalaninamide, α-methyl-N-[tricyclo[3.3.1.1^{3,7}]-
dec-2-yloxy)carbonyl]-L-tryptophyl-ß-alanyl-</u>
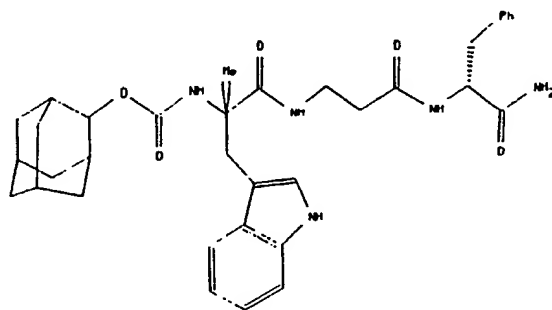
m.p. 113-118°C (MeOH/H$_2$O); [α]$_D^{20}$-30° (c=0.5, MeOH); IR
(film) 3313, 2909, 2856, 1694-1652 br. cm^{-1}; NMR
(CDCl$_3$) δ 1.45 (3H, s), 1.50 (2H, s), 1.65-2.00 (12H,
m), 2.14 (2H, s), 2.90 (1H, dd, J 14 and 8 Hz), 3.06
(1H, d, J 14 and 5.5 Hz), 3.2-3.4 (4H, m), 4.56 (0.5H,
d, J 7.5 Hz), 4.60 (0.5H, d, J 7.5 Hz), 4.80 (1H, s),
5.54 (1H, s), 6.14 (1H, s), 6.70 (1H, s), 6.87 (1H,
s), 7.00-7.30 (10H, m), 7.51 (1H, d, J 8 Hz), 8.87
(1H, s); FAB MS 636.4 (100), 614.4 (61); Anal.
C$_{35}$H$_{43}$N$_5$O$_5$·0.5H$_2$O; C, H, N.

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EXAMPLE 29

12-Oxa-2,5,9-triazatridecanoic acid, 3-(1H-indol-3-
ylmethyl)-3-methyl-4,8,11-trioxo-10-(phenylmethyl)-,
tricyclo[3.3.1.1^{3,7}]dec-2-yl ester, [R-(R*,R*)]- (See
Scheme 6, No. 49)
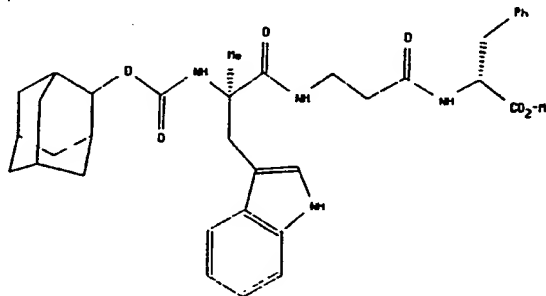
In a manner similar to Example 30, the following
was prepared, m.p. 86-90°C (foam); $[\alpha]_D^{20}$ + 17.4°
(c=0.5, MeOH); IR (film) 1738, 1698, and 1656 cm^{-1};
NMR (CDCl$_3$) δ 1.55 (3H, s), 1.50-1.60 (2H, br s),
1.65-2.05 (12H, m), 2.10-2.35 (2H, m), 2.99 (1H, dd, $\underline{J}$
14 and 8 Hz), 3.11 (1H, dd, $\underline{J}$ 14 and 5 Hz), 3.20-3.30
(1H, m), 3.31 (2H, s), 3.55-3.65 (1H, m), 3.68 (3H,
s), 4.73 (1H, dd, $\underline{J}$ 13 and 8 Hz), 4.80 (1H, s), 5.33
(1H, s), 6.40-6.60 (1H, br s), 6.90 (1H, br s), 6.98
(1H, d, $\underline{J}$ 2 Hz), 7.05-7.35 (8H, m), 7.59 (1H, d, $\underline{J}$
8 Hz), 8.45 (1H, s); MS FAB m/e 629.2 (100); Anal.
C$_{36}$H$_{44}$N$_4$O$_6$·0.25H$_2$O; C, H, N.

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EXAMPLE 30

L-Phenylalanine,N-[N-[α-methyl-N-[(tricyclo[3.3.1.1^{3,7}]
dec-2-yloxy)carbonyl]-d-tryptophyl]-ß-alanyl]-
phenylmethyl ester

Step 1 (See Scheme 6, No. 39)

A solution of 2-Adamantyloxycarbonyl-α-methyl-R-
tryptophan (8.0 g, 20 mmol) in EtOAc (100 mL) was
treated with pentafluorophenol (3.68 g, 20.0 mmol) and
cooled to 0°C. Dicyclohexylcarbodiimide (4.33 g,
21.0 mmol) was then added and the mixture left to stir
for 18 hours at 0°C. After this time the mixture was
filtered and ß-alanine methyl ester (2.47 g, 240 mmol)
added and the mixture left stirring a further 18 hours
at room temperature, filtered, and the filtrate washed
with 1M HCl (3 x 30 mL), H$_2$O (2 x 30 mL), saturated
NaHCO$_3$ solution (3 x 30 mL) H$_2$O (2 x 30 mL). The
organic phase was dried over MgSO$_4$ and concentrated in
vacuo and the product crystallized from ether to give
the ester (7.8 g, 81%); IR (film) 3700-3200,
3000-2800), 2723, 1695, and 1659 cm$_{-1}$.

Step 2 (See Scheme 6, No. 41)
ß-Alanine,N-[α-methyl-N-[(tricyclo[3.3.1.1^{3,7}]dec-
2-yloxy)carbonyl]-D-tryptophyl]

The ester from Step 1 (5.20 g, 10.8 mmol) as a
solution in 1.4 dioxane (300 mL) was treated with a
solution of LiOH·H$_2$O (454 mg, 10.8 mmol) in H$_2$O
(100 mL) dropwise at room temperature and left
stirring 18 hours. 1M HCl (10.8 mL) was added and the
mixture distilled to dryness in vacuo and the residue
chromatographed over reverse phase silica gel using
70% MeOH in H$_2$O; as eluant to give the product
(3.23 g, 51%) along with starting ester (1 g); m.p.
98-103°C (MeOH/H$_2$O); [α]$_D^{20}$ + 29° (c=1, MeOH); IR

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(film) 3351, 2911, 2855, 1706, and 1658 cm^{-1}; NMR
(CDCl$_3$) δ 1.50-2.00 (17H, m), 2.39 (2H, br s), 3.26
(1H, d, J 15 Hz), 3.40-3.50 (3H, m), 4.80 (1H, s),
5.42 (1H, br s), 6.75 (1H, t, J 6 Hz), 6.99 (1H, d, J
5   2 Hz), 7.05-7.20 (2H, m), 7.33 (1H, d, J 8 Hz), 7.57
(1H, d, J 8 Hz), 8.37 (1H, s); FAB MS m/e 468 (m+1)
and 217 (100); Anal. C$_{26}$H$_{33}$N$_3$O$_5$·0.25H$_2$O; C, H, N.

Step 3

        A solution of the acid from Step 2 (467 mg,
10   1.00 mmol) and pentafluorophenol (184 mg, 1.00 mmol)
in EtOAc (50 mL) was treated with dicyclohexyl-
carbodiimide (206 mg, 1.00 mmol) at 0°C and left
18 hours. This was then filtered and S-phenyl alanine
benzyl ester (306 mg, 1.20 mmol) added and left
15   stirring 18 hours at room temperature. This was then
washed with 1M HCl (2 x 20 mL), H$_2$O (20 mL), saturated
NaHCO$_3$ solution (2 x 20 mL), and H$_2$O (20 mL). The
organic phase was dried over MgSO$_4$ and concentrated in
vacuo and the residue chromatographed over reverse
20   phase silica gel using 75% to 85% MeOH in H$_2$O as
eluants to give the product (500 mg, 71%); m.p.
75-82°C (MeOH/H$_2$O); [α]$_D^{20}$ + 28.1° (c=0.45, MeOH); IR
(film) 3324, 2908, 2855, 1737, 1698, and 1657 cm^{-1};
NMR (CDCl$_3$) δ 1.50 (3H, s), 1.50-1.55 (2H, m),
25   1.70-2.00 (12H, m), 2.10-2.30 (2H, m), 3.06 (1H, dd, J
14 and 7 Hz), 3.14 (1H, dd, J 14 and 6 Hz), 3.29 (1H,
d, J 15 Hz), 3.25-3.60 (3H, m), 4.75-4.85 (2H, m),
5.08 (1H, d, J 12 Hz), 5.15 (1H, d, J 12 Hz), 5.29
(1H, br s), 6.20-6.30 (1H, br m), 6.81 (1H, br m),
30   6.95 (1H, d, J 2 Hz), 7.00-7.35 (13H, m), 7.57 (1H, d,
J 8 Hz), 8.20 (1H, s); Anal. C$_{42}$H$_{48}$N$_4$O$_6$; C, H, N.

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EXAMPLE 31

In a manner similar to Example 30 the following
was prepared, m.p. 77-82°C (foam); $[\alpha]_D^{20}$-19.2° (c=0.5,
MeOH); IR (film) 3305, 2906-2857, 1735, 1696, and
1658 cm^{-1}; NMR (CDCl$_3$) δ 1.51 (3H, s), 1.50-1.60 (2H,
m), 1.70-2.10 (12H, m), 2.10-2.30 (2H, m), 3.01 (1H,
dd, $\underline{J}$ 14 and 8 Hz), 3.12 (1H, dd, $\underline{J}$ 14 and 5 Hz),
3.20-3.30 (1H, m), 3.31 (1H, s), 3.55-3.65 (1H, m),
4.75-4.85 (2H, m), 5.07 (1H, d, $\underline{J}$ 12 Hz), 5.15 (1H, d,
$\underline{J}$ 12 Hz), 5.28 (1H, br s), 6.30-6.50 (1H, br s),
6.80-6.90 (1H, br), 6.97 (1H, d, $\underline{J}$ 2 Hz), 7.05-7.35;
MS FAB m/e 705.2 (71) and 327.2 (100); Anal.
C$_{42}$H$_{48}$N$_4$O$_6$; C, H, N.

EXAMPLE 32

D-Phenylalanine, N-[N-[α-methyl-N-[(tricyclo-
[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-D-tryptophyl]-ß-
alanyl]-
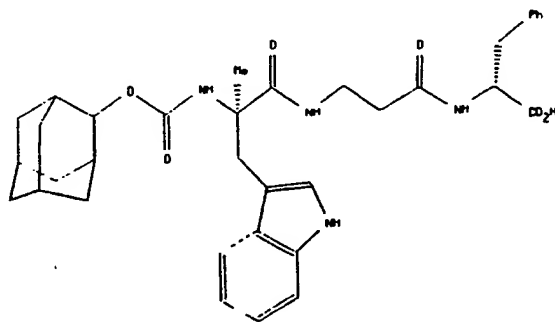
This was prepared in a manner similar to that
described in Example 33, m.p. 119-129°C (MeOH/H$_2$O);
$[\alpha]_D^{20}$ + 5.8° (c=0.5, MeOH);IR (film) 2907, 2855, 1700,
1651 cm^{-1}; NMR (CDCl$_3$ + CD$_3$OD) δ 1.53 (5H, s),
1.70-2.05 (12H, m), 2.10-2.30 (2H, br s), 2.95-3.05
(1H, m), 3.15-3.60 (5H, m), 4.65 (1H, s), 7.00-7.40

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(9H, m), 7.57 (1H, d, $\underline{J}$ 8 Hz); FAB MS m/e 615.2 (58),
216.9 (100); Anal. $C_{35}H_{42}N_4O_6 \cdot 0.5H_2O$; C, H, N.

EXAMPLE 33

S-Phenylalanine, N-[N-[α-methyl-N-[(tricyclo-
[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-R-tryptophyl]-ß-
alanyl]

A solution of the benzyl ester (450 mg, 0.64 mmol)
in absolute EtOH (100 mL) was treated with 10% Pd/C
(45 mg, 10% w/w) and put under an atmosphere of
hydrogen at 50 psi for 2 hours with agitation. The
mixture was then filtered through a filter aid and
concentrated $\underline{in\ vacuo}$ and the residue chromatographed
over reverse phase silica gel using 70% MeOH in H_2O as
eluant to yield the product as a white, noncrystalline
solid (300 mg, 76%); m.p. 114-119°C; $[\alpha]_D^{20}$ + 37.8°
(c=1), MeOH); IR (film) 3331, 2911, 2856, 1700, and
1656 cm^{-1}; NMR (CDCl$_3$) δ 1.41 (3H, s), 1.45-1.55 (2H,
m), 1.70-2.00 (12H, m), 2.10-2.20 (2H, m), 3.01 (1H,
dd, $\underline{J}$, 14 and 8 Hz), 3.15-3.50 (5H, m), 4.00-5.00 (1H,
v.br), 4.66 (1H, dd, $\underline{J}$ 13 and 7 Hz), 4.82 (1H, s),
5.46 (1H, br s), 6.50-6.70 (1H, br s), 6.87 (2H, br
s), 7.00-7.30 (8H, m), 7.52 (1H, d, $\underline{J}$ 8 Hz), 8.44 (1H,
s); Anal. $C_{35}H_{42}N_4O_6$; C, H, N.

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EXAMPLE 34

L-Phenylalanine, N-[N-[α-methyl-N-[(tricyclo-
[3.3.1.1³,⁷]dec-2-yloxy)carbonyl]-L-tryptophyl]-ß-
alanyl]-
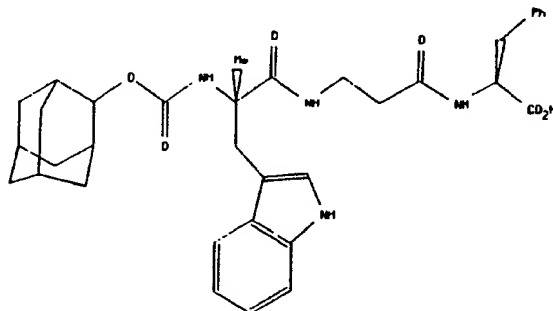
5   This was prepared in a manner similar to that
described in Example 33, m.p., 115-120°C (MeOH/H₂O);
$[\alpha]_D^{20}$-7.2° (c=0.5, MeOH); IR (film) 3391, 2906, 2854,
1700, and 1646(s) cm^{-1}; NMR (CDCl₃ + CD³OD) δ 1.51 (3H,
s), 1.54 (1H, s), 1.57 (1H, s), 1.70-2.05 (12H, m),
10   2.15-2.30 (2H, m), 2.99 (1H, dd, J 14 and 8 Hz),
3.15-3.55 (5H, m), 4.66 (1H, dd, J 8 and 5 Hz), 4.79
(1H, s, 7.00-7.40 (9H, m), 7.56 (1H, d, J 8 Hz); FAB
MS m/e 615 (100); Anal. C₃₅N₄₂N₄O₆; C, H, N.

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EXAMPLE 35
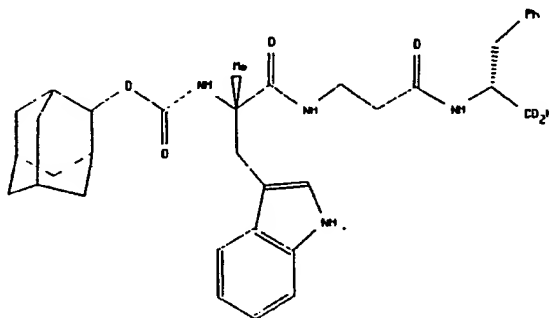
Benzenepropanoic acid, α-[[3-[[3-[(1H-indol-3-yl)-2-
methyl-1-oxo-2-[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)-
carbonyl]amino]propyl]amino]-1-oxopropyl]amino-,
[S-(R*,S*)]-

m.p., 116-124°C (MeOH/H$_2$O); [α]$_D^{20}$-35° (c=0.5, MeOH);
IR (film) 3500-3200, 2912, 2856, 1700, and 1654 cm^{-1};
NMR (CDCl^3) δ 1.42 (3H, s), 1.47 (1, s), 1.51 (1H, s),
1.65-2.20 (14H, m), 2.90-3.00 (1H, m), 3.10-3.50 (5H,
m), 3.50-4.50 (br, CO$_2$H and H$_2$O), 4.61 (1H, s), 4.82
(1H, s), 5.45 (1H, s), 6.50-6.80 (1H, br s), 6.85-7.30
(11H, m), 7.52 (1H, d, J 8 Hz), 8.58 (1H, s); FAB MS
m/e 615.2 (100; Anal. C$_{35}$H$_{42}$N$_4$O$_6$·0.4H$_2$O; C, H, N.

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EXAMPLE 36

<u>Glycine, N-[2-methyl-N-[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl-D-tryptophyl]-, phenylmethyl ester</u>
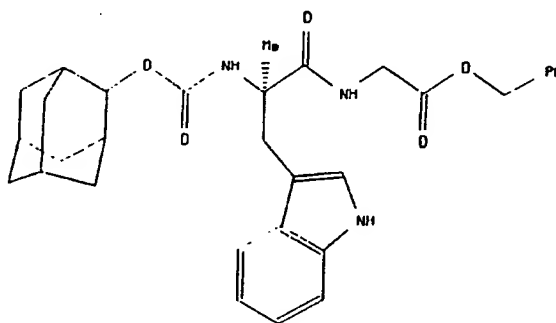
A solution of 2-Adocα-Me-<u>R</u>-TrpOH (Scheme 7, N°23b)
(3.0 g, 7.6 mmol) in EtOAc (40 mL) was treated with
pentafluorophenol (1.39 g, 7.6 mmol), and cooled to
0°C. A solution of <u>N</u>,<u>N</u>'-dicyclohexylcarbodiimide
(1.56 g, 7.6 mmol) in EtOAc (10 mL) was then added
dropwise and stirred 12 hours at 4°C and filtered.
Glycine benzyl ester hydrochloride (1.8 g, 9.0 mmol)
was added followed by the dropwise addition of
triethylamine (0.9 g, 9.0 mmol) in EtOAc (10 mL).
This was allowed to stir 18 hours at room temperature.
The reaction mixture was then washed with 1M citric
acid solution (2 x 50 mL), 1M NaHCO$_3$ solution
(2 x 50 mL) and H$_2$O (2 x 50 mL). The organic phase
was dried over MgSO$_4$ and evaporated to dryness <u>in</u>
<u>vacuo</u>. The residue was chromatographed over reverse
phase silica using 25% H$_2$O in MeOH as eluant to give
the product as a white foam (2.83 g, 68%) along with
0.9 g starting active ester, m.p. 76-82°C (foam);
[α]$_D^{20}$ + 36° (c=1, MeOH); IR (film) 3500-3200, 2908,
2855, 1745, 1702, and 1665 cm^{-1}; NMR (CDCl$_3$)
δ 1.45-1.60 (4H, m), 1.69-2.00 (13H, m), 3.30 (1H, d,
<u>J</u> 14.5 Hz), 3.50 (1H, d, <u>J</u> 14.5 Hz), 3.95-4.10 (2H,

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m), 4.84 (1H, s), 5.13 (2H, s), 5.21 (1H, s), 6.79
(1H, s), 7.01 (1H, d, $\underline{J}$ 2 Hz), 7.08 (1H, t, $\underline{J}$ 7 Hz),
7.15 (1H, t, $\underline{J}$ 7 Hz), 7.30-7.40 (6H, m), 7.57 (1H, d,
$\underline{J}$ 8 Hz), 8.26 (1H, s); FAB MS 544.4 (11), 414.3 (11),
348.2 (36), 135.2 (100); Anal.; $C_{32}H_{37}N_3O_5$; C, H, N.

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EXAMPLE 37

Carbamic acid, [2-[[2-[[1-(hydroxymethyl)-2-
phenylethyl]amino]-2-oxoethyl]amino]-1-(1H-indol-3-
ylmethyl)-1-methyl-2-oxoethyl]-, tricyclo[3.3.1.1^{3,7}]-
dec-2-yl ester, [R-(R*,S*)]- AdOC-(α-Me)DTrp-Gly-
NH((S)-1-(hydroxymethyl)-2-phenylethyl)
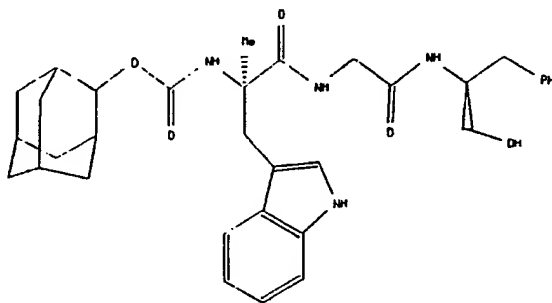
Step 1.   Glycine, N-[3-(1H-indol-3-yl)-2-methyl-1-oxo-
2-[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]amino]-
propyl-, (R)- AdOC-(α-Me)DTrp-Gly
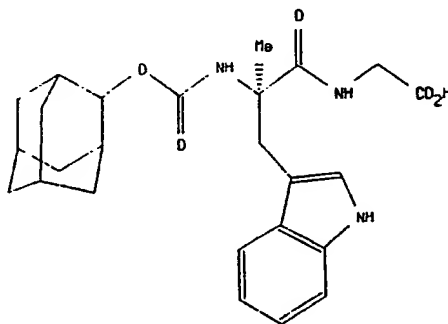
A solution of the benzyl ester (Example 36,
Scheme 7, No. 57) (2.5 g, 4.6 mmol), in absolute EtOH
(100 mL) was treated with 10% Pd/C (250 mg, 10% w/w)
and put under an atmosphere of hydrogen at 50 psi and
20°C for 5 hours with agitation. The reaction mixture
was filtered through a filter aid and the filtrate

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concentrated *in vacuo*. The residue was then
chromatographed over silica gel using 0.5% AcOH, 5%
MeOH in CH_2Cl_2 as eluant to give the product
(1.87-3 g, 90%) as a white solid; m.p. 112-117°C
5   (MeOH/H_2O); $[\alpha]_D^{20}$ +40° (c=1, MeOH); IR (film)
3500-3200, 2910, 2856, 1702, 1660, and 735 cm^{-1}; NMR
($CDCl_3$) δ 1.26 (1H, s), 1.51 (1H, s), 1.58 (3H, s),
1.70-2.00 (12H, m), 3.00-4.00 (1H, br), 3.28 (1H, d, J
14.5 Hz), 3.45 (1H, d, J 14.5 Hz), 3.94 (2H, d, J
10   5 Hz), 4.85 (1H, s), 5.35-5.50 (1H, br s), 6.85 (1H,
br t), 7.04 (1H, d, J 2 Hz), 7.05-7.18 (2H, m), 7.32
(1H, d, J 8 Hz), 7.56 (1H, d, J 8 Hz), 8.39 (1H, s);
Anal. $C_{25}H_{31}N_3O_5$; C, H, N.

Step 2

15   A solution of the acid (Scheme 7, No. 59, Step 1)
(226 mg, 0.5 mmol) and pentafluorophenol (92 mg,
0.5 mmol) in EtOAc (20 mL) was cooled to 0°C and
treated with a solution of N,N'-dicyclohexyl-
carbodiimide (108 mg, 0.525 mmol), in EtOAc (5 mL).
20   This was left 12 hour at 0°C, filtered and the
filtrate treated with S-phenylalaninol (91 mg,
0.6 mmol). This reaction mixture was stirred at room
temperature for 18 hours, evaporated to dryness *in
vacuo* and the residue chromatographed using 30%
25   n-hexane in EtOAc as eluant to give the product
(202 mg, 66%); IR (film) 3500-3200, 2911, 2855, 1695,
and 1658 cm^{-1}; NMR (CD_3OD) δ 1.44 (3H, s), 1.52-1.62
(2H, m), 1.70-2.10 (14H, m), 2.78 (1H, dd, J 13.5 and
8 Hz), 2.93 (1H, dd, J 13.5 and 6 Hz), 3.24 (1H, d, J
30   14.5 Hz), 3.41 (1H, d, J 14.5 Hz), 3.53 (2H, d, J 5.5
Hz), 3.57 (1H, d, J 17 Hz), 3.71 (1H, d, J 17 Hz),
4.05-4.15 (1H, m), 4.88 (1H, s), 6.98 (1H, dt, J 7.5
and 1 Hz), 7.00-7.25 (7H, m), 7.32 (1H, d, J 8 Hz),
7.50 (1H, d, J 8 Hz).

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EXAMPLE 39

Carbamic acid, [2-[[4-[[1-(hydroxymethyl)-2-
phenylethyl]amino]-4-oxobutyl]amino]-1-(1H-indol-3-
ylmethyl)-1-methyl-2-oxoethyl]-, tricyclo[3.3.1.1^{3,7}]-
5   dec-2-yl ester, [R-(R*,S*)]-
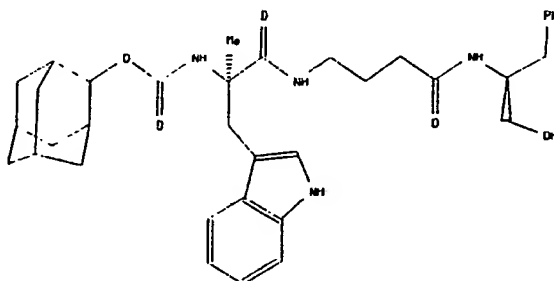
Step 1. Butanoic acid, 4-[[3-(1H-indol-3-yl)-2-
methyl-1-oxo-2-[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)-
carbonyl]amino]propyl]amino]-, (R)-
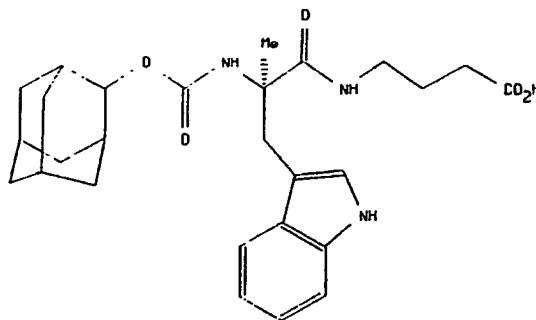
A solution of the methyl ester (Example 38,
10   Scheme 8, No. 60) (2.6 g, 5.2 mmol) in 1,4-dioxan
(500 mL) was treated dropwise with a solution of LiOH
(104 mL of a 0.05M solution, 5.20 mmol) over 24 hours
with vigorous stirring. This mixture was stirred at
room temperature for 24 hours and quenched with 1M HCl
15   (5.2 mL). The solvent was removed in vacuo and the
residue chromatographed using 0.5% AcOH, 5% MeOH in

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CH$_2$Cl$_2$ to give 80 mg of starting ester along with
1.32 g of product, 55% yield, 77% conversion, m.p.
92-96°C (CH$_2$Cl$_2$); [α]$_D^{20}$ + 29.3° (c=, MeOH); IR (film)
3600-3200, 2909, 2856, 1702, and 1651 cm^{-1}; NMR (CDCl$_3$)
δ 1.50-1.55 (2H, mn), 1.61 (3H, s), 1.62-2.00 (14H,
m), 2.10-2.25 (2H, m), 3.20-3.40 (2H, m), 3.24 (1H, d,
J 14.5 Hz), 3.45 (1H, d, J 14.5 Hz), 4.84 (1H, s),
5.47 (1H, s), 6.58-6.65 (1H, br m), 7.03 (1H, d, J
2 Hz), 7.09 (1H, t, J 7 Hz), 7.17 (1H, t, J 7 Hz),
7.35 (1H, d, J 8 Hz), 7.57 (1H, d, J 8 Hz), 8.59 (1H,
s); Anal. C$_{27}$H$_{35}$N$_3$O$_5$·0.2$_H$2O; C, H, N.

Step 2

A solution of the acid (Step 1, Scheme 8, No. 61)
(240 mg, 0.5 mmol), and pentafluorophenol (92 mg,
0.8 mmol) in EtOAc (20 mL) was cooled to 0°C and
treated with a solution of N,N'-dicyclohexyl-
carbodiimide (108 mg, 0.55 mmol) in EtOAc (5 mL).
This mixture was left at 0°C for 12 hours, filtered,
and the filtrate treated with S-phenylalaninol. This
reaction mixture was left stirring at room temperature
for 24 hours, the solvent removed in vacuo, and the
residue chromatographed using 10% MeOH in CH$_2$CL$_2$ as
eluant to give the product as a white solid (153 mg,
50%); IR (film) 3500-3200, 207, 2850, 1692, and
1642 cm^{-1}; NMR (CD$_3$OD) δ 1.43 (3H, s), 1.50-1.70 (4H,
m), 1.75-1.95 (8H, m), 2.00-2.15 (6H, m), 2.7s (1H,
dd, J 14 and 8 Hz), 2.91 (1H, dd, J 14 and 6 Hz),
2.95-3.35 (3H, m), 3.45-3.50 (3H, m), 4.07-4.17 (1H,
m), 4.81 (1H + HOD), 6.93-7.09 (3H, m), 7.10-7.30 (5H,
m), 7.31 (1H, d, J 8 Hz), 7.53 (1H, d, J 8 Hz).

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EXAMPLE 40

Tricyclo[3.3.1.1³,⁷]dec-2-yl-(±)-[3-(1H-indol-3-yl-
methyl)-2,5-dioxo-1-(2-phenylethyl)-3-pyrrolidinyl]-
carbamate (68)

Step 1.   Methyl-(±)-ß-amino-ß-[(phenylmethoxy)-
carbonyl]-1H-indole-3-butanoate (64)

        1-Methyl-(±)-ß-cyano-1-[1,1-dimethylethoxy)-
carbonyl]-1H-indole-3-butanoate (63) (0.241 g,
0.50 mmol) was dissolved in ethanol (5 mL). The
solution cooled to -5°C in an acetone-ice bath and
ethanolic HCl was added dropwise. H_2O (0.1 mL) was
added and the reaction was warmed to room temperature.
The solution was left to stir for 24 hours, and the
solvent evaporated off in vacuo. The oil was
dissolved in ethyl acetate (50 mL) and washed with 10%
Na_2CO_3 (50 mL) solution. The organic layer was dried
($MgSO^4$), filtered, and evaporated to dryness. The
product was isolated by flash chromatography (ethyl
acetate:hexane, 1:1) to yield the wanted product.
(0.120 g, 67%) as a yellow oil, v_{max} (cm⁻¹, thin film)
3350 (NH); 3425 (NH br); 1741 (CO ester), H (300 M Hz,
$CDCl_3$), δ 2.12 (2H, brs, NH_2); 3.17 (1H, d, J 18 Hz,
$C\underline{H}_2CO_2CH_3$); 3.28 (1H, d, J 18 Hz, $C\underline{H}_2CO_2CH_3$); 3.37 (1H,
d, J 15 Hz, indole-$C\underline{H}_2$); 3.43 (3H, s, OCH_3); 3.53 (1H,
d, J 15 Hz, indole-$C\underline{H}_2$); 4.82 (1H, d, J 12 Hz, $C\underline{H}^2Ph$);
4.92 (1H, d, J 12 Hz, $C\underline{H}_2Ph$); 6.73 (1H, d, J 2 Hz,
2-H); 6.95-7.21 (8H, m, 5-H + 6-H + 7-H + H_{arom}); 7.47
(1H, s, 4-H); 8.42 (1H, s, NH).

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Step 2.   Methyl-(±)-ß-[(phenylmethoxy)carbonyl]-ß-
[(tricyclo-[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-
amino]-1H-indole-3-butanoate (65)

         Methyl-(±)-ß-amino-ß-[(phenylmethoxy)carbonyl]-
 5   1H-indole-3-butanoate (64) (120 mg, 0.33 mmol) was
       dissolved in dry THF (10 mL) under argon.
       Triethylamine (55 µL, 0.40 mmol) was injected. The
       solution was cooled to 0°C in an ice- alt bath and
       2-adamantyl chloride (77 mg, 0.36 mmol) dissolved in
10   THF (5 mL) was injected. The solution was stirred for
       12 hours at room temperature before triethylamine
       hydrochloride was filtered off. Dichloromethane
       (50 mL) was added and the solution was washed with
       water (2 x 25 mL). The organic payer was dried
15   (MgSO$_4$), filtered, and evaporated to dryness. The
       product was isolated by flash chromatography (ether:
       hexane, 1:1), to furnish the title compound (105 mg,
       58%), m.p. 61.5-62.5°C. υ_{max}: (cm^{-1}, thin film) 3412
       (NH), 1738 (CO), H (300M Hz, CDCl$_3$), 1.49-2.09 (14H,
20   m, adamantyl-H); 3.12 (1H, d, $\underline{J}$ 15 Hz, C$\underline{H}$H$_2$CO$_2$CH$_3$);
       3.30 (1H, d, $\underline{J}$ 15 Hz, CH$_2$CO$_2$CH$_3$); 3.38 (s, 3H, OCH$_3$);
       3.72 (1H, d, $\underline{J}$ 15 Hz, indole-C$\underline{H}$^{2}); 3.80 (1H, d, $\underline{J}$
       15 Hz, indole-C$\underline{H}$^{2}); 4.83 (1H, brs, C$\underline{H}$); 4.98 (1H, d, $\underline{J}$
       112 Hz, PhC$\underline{H}$$_2$); 5.11 (1H, d, $\underline{J}$ 12 Hz, PhC$\underline{H}$$_2$); 6.88
25   (1H, s, NH); 6.79 (1H, s, 2-H); 7.03 (1H, t, $\underline{J}$ 7 Hz,
       6-H); 7.14 (1H, t, $\underline{J}$ 7 Hz, 5-H); 7.17-7.34 (6H, m,
       7-H, H$_{arom}$), 7.48 (1H, d, J-8 Hz, 4-H), 8.30 (1H, s,
       NH). m/z (FAB) 545 (M+1); 501; 130. Found: C,
       70.6%; H, 6.8%; N, 5.0%; C$_{32}$H$_{36}$N$_2$O$_6$ requires C, 70.6%;
30   H, 6.7%; N, 5.1%).

Step 3.   Methyl-(±)-ß-carboxy-ß-[[(tricyclo-
[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]amino]-1H-indole-3-
butanoate (66)

In a 250-mL glass vial, methyl-(±)-ß-[(phenyl-
methoxy)carbonyl]-ß-[[(tricyclo[3.3.1.1^{3,7}]dec-
2-yloxy)carbonyl[amino]-1H-indole-3-butanoate (65)
(105 mg, 0.19 mmol). Palladium on charcoal (10%, Ca
20 mg) and ethanol (75 mL) was added. The vessel was
sealed in a Parr Hydrogenation Apparatus and charged
with H_2 gas (45 psi). Shaking was initiated after
pressurization and continued for 12 hours. Upon
completion, palladium on charcoal (10%) was filtered
of and the filtrate evaporated to dryness. The
product was isolated by flash chromatography
(methanol: water, 2:1) to yield a white powder (77 mg,
88%), m.p. 108-9°C. v_{max} (cm^{-1}, thin film) 3413 (NH);
1733 (CO). δ H (300M Hz, CDCl$_3$), 1.47-2.07 (14H, m,
adamantyl-H); 3.14 (1H, d, J 16 Hz, C$\underline{H}_2$CO$_2$CH$_3$); 3.26
(1H, d, J 16 Hz, C$\underline{H}_2$CO$_2$CH$_3$); 3.64 (3H, s, OCH$_3$); 3.76
(1H, d, J 15 Hz, indole-CH^2); 3.84 (1H, d, J 15 Hz,
indole-C$\underline{H}_2$); 4.83 (1H, brs, CH); 5.75 (1H, brs, O$\underline{H}$);
5.96 (1H, s, NH); 6.98-7.04 (2H, m, 2-H + 6-H); 7.10
(1H, t, J 7 Hz, 5-H); 7.28' (1H, d, J 8 Hz, 7-H); 7.61
(1H, d, J 8 Hz, 4-H); 8.34 (1H, s, NH). δ c (75.5M Hz,
CDCl$_3$) 27.0, 27.2 31.3, 31.7, 32.1, 36.4, 37.4, 39.7,
51.8, 62.4, 78.0, 108.9, 111.1, 118.7, 119.4, 121.7,
124.1, 128.2, 135.7, 154.8, 171.3, 176.2. m/z (FAB)
455 (M+1), 411, 217, 135, 130. Found: C, 65.7%; H,
6.7%; N, 6.0%. C$_{25}$H$_{30}$N$_2$O$_6$ requires C, 66.1%; H, 6.65%;
N, 6.2%.

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Step 4.   Methyl-(±)-ß-[[(2-phenylethyl)amino]carbonyl-
ß-[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]amino]-
1H-indole-3-butanoate (67)

Methyl-(±)-ß-[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)-
carbonyl[amino]-1H-indole-3-butanoate (66) (200 mg,
0.44 mmol) was dissolved followed by
dicyclohexylcarbodiamide (100 mg, 0.48 mmol). The
solution was left stirring for 2 hours before
phenylethylamine (60 mg, 0.50 mmol) was injected to
the solution. The mixture was left stirring
overnight. The solution was evaporated down to
dryness, ethyl acetate added, and dicyclohexylurea
filtered off. The filtrate was evaporated down to
dryness and the product was isolated by flash
chromatography (hexane:ethyl acetate, 3:1) to give a
white solid (180 mg, 73%), m.p. 78.0-79.5°C. υ_{max} (cm^{-1}, thin film), 3333 (NH), 1730 (CO), 1659 (CO amide),
H (300M Hz, CDCl$_3$), δ 1.51-2.04 (14H, m, adamantyl-H);
2.61 (2H, m, C$\underline{H}_2$NH); 2.94 (1H, d, $\underline{J}$ 16 Hz, C$\underline{H}^2$CO$_2$CH$_3$);
3.21 (1H, d, $\underline{J}$ 16 Hz, C$\underline{H}_2$CO$_2$CH$_3$); 3.37 (1H, d, $\underline{J}$ 7 Hz,
C$\underline{H}_2$Ph); 3.41 (1H, d, $\underline{J}$ 7 Hz, C$\underline{H}_2$Ph); 3.46 (1H, d, $\underline{J}$
15 Hz, indole-C$\underline{H}_2$); 3.57 (1H, d, $\underline{J}$ 15 Hz, indole-C$\underline{H}_2$);
3.62 (3H, s, OCH$_3$); 4.78 (1H, brs, C$\underline{H}$); 5.88 (1H, brs,
NH urethane); 6.58 (1H, brs, NH amide); 6.92 (1H, d, $\underline{J}$
2 Hz, 2-H); 7.03-7.26 (7H, m, 5-H + 6-H + H$_{arom}$); 7.33
(1H, d, $\underline{J}$ 8 Hz, 7-H); 7.56 (1H, d, $\underline{J}$ 8 Hz, 4-H). mz/
(FAB). 558 (M+1), 362, 331, 231, 135, 130, 105.
(Found: C, 69.0; H, 6.8; N, 7.2. C$_{33}$H$_{39}$N$_3$O$_5$·0.75H$_2$O
requires C, 69.4; H, 7.1; N, 7.4).

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<u>Step 5. Tricyclo[3.3.1.1^{3,7}]dec-2-yl-(±)-[3-(1H-indol-
3-yl-methyl)-2,5-dioxo-1-(2-phenylethyl)-
3-pyrrolidinyl]-carbamate (68)</u>

The ester (67) above (110 mg, 0.20 mmol) was
dissolved in 20 mL THF and cooled to 0°C. Lithium
hydroxide (21 mL, 0.01 M) was added dropwise to the
solution over a 3-hour period. The solution was kept
stirring for a further 1 hour and then allowed to warm
to room temperature. Hydrochloric acid (2.1 mL,
0.1 M) was added and the solution extracted with ethyl
acetate (3 x 20 mL). The organic layers were
combined, dried with MgSO$_4$, filtered, and evaporated
to dryness, to afford (105 g, 98%) of crude product.
The product was isolated by flash chromatography
(methanol:water, 4:1) as a white powder (84 mg,
78.5%). v_{max} (cm^{-1}, thin film). 3347 (NH), 2912 (CH);
1781 (CO), 1701 (CO). H (300M Hz, CDCl$_3$) δ 1.55-1.97
(14H, m, adamantyl-H); 2.38 (2H, m, NHC$\underline{H}_2$); 3.00 (1H,
d, J 18 Hz, C$\underline{H}_2$CON); 3.05 (1H, d, J 15 Hz,
indole-C$\underline{H}_2$); 3.47 (2H, t, J 8 Hz, C$\underline{H}^2$Ph); 4.80 (1H, s,
C$\underline{H}$); 5.49 (1H, s, NH); 7.04-7.35 (8H, m, 5-H + 6-H +
7H + H$_{arom}$; 7.56 (1H, d, J 8 Hz, 4-H); 8.68 (1H, s,
NH). C (75.5M Hz, CDCl$_3$), 26.9, 27.1, 31.7, 32.0,
36.3, 37.3, 39.8, 40.2, 59.95, 76.4, 107.3, 111.4,
118.6, 120.2, 122.7, 123.7, 126.4, 127.4, 128.7,
136.0, 138.0, 154.9, 174.1, 176.1. m/z (C.I.) 528
(M+1). 527, 526, 374, 331, 130. Found: C, 72.6%; H,
6.7%; N, 7.9%; C$_{32}$H$_{35}$N$_3$O$_4$0.25H$_2$O requires C, 72.5%; H,
6.7%; N, 7.9%).

EXAMPLE 41

<u>(R^2 = Me, see Scheme 15a)</u>

A suspension of powdered sodium hydroxide (2 g,
50 mmol) and ethyl 2-cyanopropionate (20 g, 157 mmol)
in 150 mL toluene was heated under nitrogen atmosphere

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to 100°C and gramine (30.1 g, 172 mmol) added in
portions. After 30 minutes the temperature was raised
to 130°C (oil bath) and the mixture gently refluxed
for 16 hours. Then 100 mL water and 200 mL ethyl
5   acetate were added, the mixture neutralized with
acetic acid, the organic layer separated, washed with
water (100 mL), dried (sodium sulfate) and evaporated.
The residue was purified by chromatography over silica
gel using toluene/ethyl acetate (1:1, v/v, Rf 0.4).
10 2a was isolated as a light brown viscous oil (34.5 g,
86%). MS (70eV): m/z 256 (M^+, 8%), 130 (100%).

EXAMPLE 42

(R^2 = Me, see Scheme 15a)

    Compound 2a (5 g, 19.5 mmol) in 250 mL dioxane,
15 saturated with ammonia, was hydrogenated (100 bar,
80°C) with Raney nickel alloy (0.95 g) in an autoclave
for 1 hour. After filtration and evaporation the
residue was purified by chromatography over silica gel
using dichloromethane/methanol (95:5, v/v, Rf 0.1).
20 3a was isolated as a colorless viscous oil (4.76 g,
94%). MS (70eV): m/z 260 (M^+, 17), 130 (100), 117
(48).

EXAMPLE 43

(R^1 = 2-adamantyl, R^2 = Me, see Scheme 15a)

25   To a stirred solution of 2-adamantylchloroformate
(4.45 g, 20.7 mmol) in dry THF (50 mL) under N_2
atmosphere was added a solution of 3a (4.76 g,
18.3 mmol) in dry THF (100 mL) followed by a solution
of triethylamine (3.7 g, 36.6 mmol) in dry THF (50 mL)
30 dropwise. After 15 minutes the reaction mixture was
filtered, the solvent removed and the residue column
chromatographed on silica gel using CH_2Cl_2/MeOH (98:2)

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as eluents to yield 4a as a colorless amorphous solid
(7.8 g, 97%). MS (70eV): m/z 438 (M^+, 20), 130 (100).

EXAMPLE 44

(R^1 = 2-adamantyl, R^2 = Me, see Scheme 15a)

To a solution of 4a (3.9 g, 8.9 mmol) in
dioxane/H_2O 2:1 (60 mL) was added an excess of LiOH
(0.325 g, 13.5 mmol) and stirred at room temperature
for 72 hours. After removing the solvent in vacuo the
residue was suspended in water (50 mL), neutralized
with acetic acid, extracted with CH_2Cl_2 and the
organic layer separated and dried (sodium sulfate).
After filtration and evaporation the residue was
chromatographed using CH_2Cl_2/MeOH 95:5 (v/v, Rf 0.3)
as eluents to yield the acid 5a as a colorless,
amorphous solid (2.5 g. 69%). MS (70eV): m/z 410
(M^+, 4), 130(100).

EXAMPLE 45

(R^1 = 2-adamantyl, R^2 = Me, R^3 = -CH$_2$OH, c = 1, R^4 = H,
see Scheme 15a)

Carbamic acid, [3-[[1-(hydroxymethyl)-2-
phenylethyl]amino]-2-(1H- indol-3-ylmethyl)-2-methyl-
3-oxopropyl]-, tricyclo[3.3.1.1^{3,7}] dec-2-yl ester [S-
(R*,RS)]-

To a solution of 5a (1 g, 2.44 mmol) in dry ethyl
acetate (40 mL) was added pentafluorophenol (0.45 g,
2.44 mmol) and stirred for 10 minutes. The reaction
mixture was cooled to 0°C and a solution of
dicyclohexylcarbodiimide (0.505 g, 2.44 mmol) in ethyl
acetate (10 mL) was added dropwise. This solution was
stirred for one hour at 0°C then at room temperature
for four hours before leaving it at 4°C overnight.
The mixture was filtered and the precipitate washed
with cold ethyl acetate (10 mL) and a solution of (S)-

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(-)-phenylalaninol (0.405 g, 2.68 mmol) in ethyl
acetate (25 mL) was added dropwise to the combined
filtrates. The mixture was left to stir for 4 days at
room temperature. The reaction mixture was diluted

5   with ethyl acetate (100 mL), washed with water
(100 mL), dried (sodium sulfate) and evaporated. The
residue was chromatographed on silica gel using
CH_2Cl_2/MeOH (98:2) as eluants to yield 6a as a
colorless amorphous solid (0.780 g, 59%, mixture of

10   two diastereomers), m.p. 85-95°C. CI-MS (70eV, NH3):
m/z 544 (MH^+, 100), 392 (76).

In an analogous manner Examples 46-57 are prepared:
(C* = configuration at the chiral C-atom of the
substituted 2-phenylethylamide residue, R^2 center is

15   always RS)

                        EXAMPLE 46
       (R^1 = (1S)-2-bornyl, R^2 = Me, R^3 = R^4 = H, c = 1)
       Carbamic acid, [2-(1H-indol-3-ylmethyl)-2-methyl-3-
       oxo-3-[(2-phenylethyl)amino]propyl-, 1,7,7-

20   trimethylbicyclo[2.2.1] hept-2-yl ester (Bicyclo
       system is 1S-endo, chain center is RS)
       m.p. 60-70°C, MS (70eV): m/z 515 (M^+,5), 130 (100)

                        EXAMPLE 47
       (R^1 = 1-adamantyl, R^2 = Me, R^3 = R^4 = H, c = 1)
25   Carbamic acid, [2-(1H-indol-3-ylmethyl)-2-methyl-3-
       oxo-3-[(2-phenylethyl)amino]propyl-, tricyclo-
       [3.3.1.1^{3,7}]dec-1-yl ester, (±)-
       m.p. 75-85°C, MS (70eV): m/z 513(M+,100), 305(91)

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EXAMPLE 48

(R^1 = 2-adamantyl, R^2 = Me, R^3 = R^4 = H, c = 1)
Carbamic acid, [2-(1H-indol-3-ylmethyl)-2-methyl-3-
oxo-3-[(2- phenylethyl)amino]propyl]-,
tricyclo[3.3.1.1^{3,7}]dec-2-yl ester, (±)-
m.p. 75-85°C, MS (70eV): m/z 513 (M$^+$,25), 305 (88),
134 (100)

EXAMPLE 49

(R^1 = (1S)-2-bornyl, R^2 = Me, R^3 = CH_2OH, R^4 = H,
c = 1, C* = S)
Carbamic acid, [3-[[1-(hydroxymethyl)-2-
phenylethyl]amino]-2-(1H-indol-3-ylmethyl)-2-methyl-3-
oxopropyl]-1,7,7-trimethylbicyclo [2.2.1]hept-2-yl
ester (Bicyclo system is 1S-endo, hydroxymethyl center
is S, other center is RS)
m.p. 75-85°C, MS (70eV): m/z 545 (M$^+$,7), 130 (22), 95
(77), 44 (100)

EXAMPLE 50

(R^1 = 2-adamantyl, R^2 = Me, R^3 = H,
R^4 = $NHCOCH_2CH_2CO_2Bz$, c = 1, C* = R)
14-Oxa-2,6,9-triazapentadecanoic acid, 4-(1H-indol-3-
ylmethyl-4-methyl-5,10,13-trioxo-8,15-diphenyl-,
tricyclo[3.3.1.1^{3,7}]-dec-2-yl ester, [R-(R*,R*)]-
m.p. 80-90°C, CI-MS (CH_4): m/z 611 (21), 459 (21), 135
(100)

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EXAMPLE 51

(R^1 = 2-adamantyl, R^2 = Me, R^3 = H,
R^4 = NHCOCH = CHCO$_2$Me, c = 1, C* = R)
14-Oxa-2,6,9-triazapentadec-11-enoic acid, [4-(1H-
indol-3-yl-methyl)-4-methyl-5,10,13-trioxo-8-phenyl-,
tricyclo[3.3.1.1^{3,7}] dec-2-yl ester, [R-[R*,R*-(E)]-
m.p. 105-120°C, CI-MS (CH$_4$): m/z 641 (MH$^+$, 1), 151
(18), 135 (100)

EXAMPLE 52

(R^1 = 2-adamantyl, R^2 = Me, R^3 = H, R^4 = NHCO$_2$-t-Bu,
c = 1, C* = R)
11-Oxa-2,6,9-triazatridecanoic acid, 4-(1H-indol-3-
ylmethyl)-4,12,12-trimethyl-1,5,10-trioxo-8-phenyl-,
tricyclo[3.3.1.1^{3,7}] dec-2-yl ester, [R-(R*,R*)]-
m.p. 100-110°C, CI-MS (CH$_4$): m/z 629 (MH$^+$, 8), 135
(100)

EXAMPLE 53

(R^1 = 2-adamantyl, R^2 = Me, R^3 = H,
R^4 = NHCOCH$_2$CH$_2$CO$_2$H, c = 1, C* = R)
Butanoic acid, 4-[[2-[[2-(1H-indol-3-ylmethyl)-2-
methyl-1-oxo-3-[[(tricyclo[3.3.1.1^{3,7}]dec-2-
yloxy)carbonyl]amino]-propyl]amino]-1-
phenylethyl]amino]-4-oxo-, [R-(R*,R*)]-
m.p. 110-125°C, CI-MS (CH$_4$): m/z 628 (M$^-$,21), 164
(100)

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EXAMPLE 54

(R^1 = 2-adamantyl, R^2 = Me, R^3 = H, R^4 = NHCOCH = CH-CO$_2$H, c = 1, C* = R)

2-Butenoic acid, 4-[2-[[2-(1H-indol-3-ylmethyl)-2-methyl-1-oxo-3-[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]amino]-propyl]amino]-1-phenylethyl]-4-oxo- (Trp center RS; other center R; double bond E)

m.p. 210-220°C, CI-MS (CH$_4$): m/z 626 (M$^-$,7), 474 (100), 164 (88)

EXAMPLE 55

(R^1 = 2-adamantyl, R^2 = Me, R^4 = H, c = 0)

Carbamic acid, [2-(1H-indol-3-ylmethyl)-2-methyl-3-oxo-3-[(phenyl methyl)amino]propyl]-, tricyclo[3.3.1.1^{3,7}]dec-2-yl ester, (±)-

m.p. 80-90°C, MS (70eV): m/z 499 (M$^+$,25), 291 (47), 130 (100)

EXAMPLE 56

(R^1 = (1S)-2-bornyl, R^2 = Me, R^3 = CH$_2$OCOCH$_2$CH$_2$CO$_2$H, R4 = H, c = 1, C* = S)

Butanedioic acid, mono 2-[[2-(1H-indol-3-ylmethyl)-2-methyl-1-oxo-3-[[(1,7,7-trimethylbicyclo[2.2.1]hept-2-yloxy)carbonyl]-amino]propyl]amino]-3-phenylpropyl ester (Bicyclo system is 1S-endo, phenylmethyl center is S, other center is RS)

m.p. 115-130, CI-MS (CH$_4$): m/z 646 (MH$^+$, 34), 528 (78), 101 (100)

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EXAMPLE 57

$(R^1 = 2\text{-adamantyl}, R^2 = Me, R^3 = CH_2OCOCH_2CH_2CO_2H,$
$R^4 = H, c = 1, C^* = S)$
Butanedioic acid, [2-[[2-(1H-indol-3-ylmethyl)-2-
methyl-1-oxo-3-[[(tricyclo[3.3.1.1^{3,7}]dec-2-
yloxy)carbonyl]amino]propyl]-amino]-3 phenylpropyl
ester (Trp center RS; other center S)
m.p. 85-95°C; CI-MS (C_4H_{10}): m/z 643 (M⁻, 16), 642
(19), 235 (100)

The conversion of compound 5a $(R^1 = 2\text{-adamantyl},$
$R^2 = Me)$ to the compounds 6f, 6g, 6h, 6i, 6k, and the
conversion of compounds 6a and 6e to the compounds 6m
and 6n has been done in analogy to already described
procedures. Compounds of general formula Ia, where
R^2, R^3 and R^4 are H are also prepared according to
synthetic scheme 15b:

EXAMPLE 58

(c = 1, see Scheme 15b)
A solution of N-(β-phenylethyl)cyanoacetamide (8a,
18.8 g, 0.1 mol), indole-3-carboxaldehyde (14.5 g,
0.1 mol) and piperidine (5 drops) in ethanol (100 mL)
was refluxed for 16 hours. After cooling to room
temperature the precipitate was filtered off, washed
with ethanol (2 x 20 mL) and dried to give 9a as
yellow crystals (29 g, 92%). MS (70eV): m/z 315
(M⁺,14), 195 (100).

EXAMPLE 59

(c = 1, see Scheme 15b)
Compound 9a (3.15 g, 10 mmol) in 50 mL dioxane,
saturated with ammonia, was hydrogenated (100 bar,
80°C) with Raney nickel alloy (0.5 g) in an autoclave
for 17 hours. After filtration and evaporation the

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residue was chromatographed on silica gel using
CH₂Cl₂/MeOH 9:1 (v/v) as eluents. 10a was obtained as
colorless crystals from ethyl acetate (1.16 g, 36%).
MS (70eV): m/z 321 (M⁺, 46), 170 (93); 130 (100).

5   EXAMPLE 60
(R¹ = 2-adamantyl, c = 1, see Scheme 15b)
Carbamic acid, [2-(1H-indol-3-ylmethyl)-3-oxo-3-[(2-
phenylethyl)amino]propyl]-, tricyclo[3.3.1.1³,⁷]dec-2-
yl ester, (±)-
10   The conversion of 10a to 11a was done according to
the conversion of 3a to 4a. After chromatographic
separation using CH₂Cl₂/MeOH 98:2 as eluents 11a was
isolated as a colorless amorphous solid (87%), m.p.
115-140°C. MS (70eV): m/z 499 (M⁺, 3), 291 (100).

15   EXAMPLES 61 AND 62
(c = 1, see Scheme 15c)
        A suspension of powdered sodium hydroxide (0.5 g,
12.5 mmol) and N-(β-phenylethyl)cyanoacetamide (8a,
8 g, 42.5 mmol) in 50 mL toluene was heated under
20   nitrogen atmosphere to 100°C and gramine (7.4 g,
42.5 mmol) added in portions. After 30 minutes the
temperature was raised to 130°C (oil bath) and the
mixture gently refluxed for 2 hours. Then 50 mL water
and 200 mL ethyl acetate were added, the mixture
25   neutralized with acetic acid, the organic layer
separated, washed with water (100 mL), dried (sodium
sulfate) and evaporated. The residue was separated by
chromatography on silica gel using CH₂Cl₂/EtOAc 9:1
(v/v) as eluents.
30   1. fraction: compound 13a as colorless crystals
(4.5 g, 47%) MS (70eV): m/z 446 (M⁺, 4), 130 (100).
        2. fraction: compound 12a, colorless crystals from

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ethanol (3.05 g, 23%). MS (70eV): m/z 317 (M$^+$, 18),
130 (100).

EXAMPLE 63

(R^1 = 2-adamantyl, c = 1)
Carbamic acid, [2,2-bis(1H-indol-3-ylmethyl)-3-oxo-3-
[(2-phenylethyl)amino]propyl]-, tricyclo[3.3.1.1^{3,7}]-
dec-2-yl ester

The conversion of 13a (c = 1) to 17a (R^1 = 2-
adamantyl, c = 1) was completed in analogy to the
conversion of 2a to 4a. After purification by
chromatography on silica gel using CH$_2$Cl$_2$/MeOH 98:2
17a was isolated as a colorless amorphous solid (yield
50% from 13a), m.p. 105-110°C. CI-MS (NH$_3$): m/z 629
(MH$^+$, 100%).

EXAMPLE 64

(R^1 = 1-adamantyl, R^2 = Me, see Scheme 16)
To a stirred solution of 3a (3 g, 11.5 mmol) in
anhydrous THF (100 mL) at room temperature was added
adamantane-1-carbonyl chloride (2.28 g, 11.5 mmol),
followed by a solution of triethylamine (3.2 mL,
23 mmol) in THF (20 mL) dropwise. The reaction was
complete after 30 minutes as assayed by thin layer
chromatography. The reaction mixture was filtered and
the solvent removed in vacuo. The residue was
purified by chromatography over silica gel using
CH$_2$Cl$_2$/MeOH 98:2 as eluents. 18a was isolated as a
colorless amorphous solid (3.25 g, 67%). MS (70eV):
m/z 422 (M$^+$, 35), 293 (34), 130 (100).

EXAMPLE 65

(R^1 = 1-adamantyl, R^2 = Me, see Scheme 16)
To a solution of 18a (3.25 g, 7.7 mmol) in 1.4-
dioxane/H$_2$O (2:1, 90 mL) was added an excess of LiOH

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(0.37 g, 15.4 mmol) and the solution stirred at room
temperature for 48 hours. After removing the solvent
in vacuo the residue was dissolved in water (150 mL),
acidified with citric acid (10% in water) and
extracted with dichloromethane (2 x 100 mL). The
organic layer was dried (Na$_2$SO$_4$) and evaporated. 19a
was isolated as a colorless, amorphous solid (3 g,
≈100%). TLC (silica gel): Rf 0.2 (CH$_2$Cl$_2$/MeOH 95:5).

EXAMPLE 66
(R^1 = 1-adamantyl, R^2 = Me, R^3 = -CH$_2$OH, c = 1, R^4 = H,
see Scheme 16)
1H-Indole-3-propanamine, N-[1-(hydroxymethyl)-2-
phenylethyl]-∝- methyl-∝-[[(tricyclo[3.3.1.1^{3,7}]dec-2-
ylcarbonyl)amino]methyl]- (indole center is RS, other
center is S)
    The conversion of 19a to 20a was done in analogy
to the conversion of 5a to 6a. After purification by
chromatography on silica gel using CH$_2$Cl$_2$/MeOH 98:2
20a was isolated as a colorless amorphous solid (52%),
m.p. 85-95°C. MS (70eV): m/z 527 (M$^+$,30), 335 (100).

There is obtained in an analogous manner:

EXAMPLE 67
(R^1 = 1-adamantyl, R^2 = Me, R^3 = H, c = 1, R^4 = H)
1H-Indole-3-propanamide, ∝-methyl-N-(2-phenylethyl)-∝-
[[(tricyclo[3.3.1.1^{3,7}]dec-2-ylcarbonyl)amino]methyl],
(±)-
    A colorless amorphous solid, m.p. 80-90°C. MS
(70eV): m/z 497 (M$^+$,9), 305 (43), 184 (56), 135 (64),
130 (100).

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EXAMPLE 68

(See Scheme 17)

In an autoclave 1-(3'-indolyl)-butan-3-one
(12.32 g, 65.9 mmol), potassium cyanide (4.7 g,
5   72.3 mmol), ammonium carbonate (6.9 g, 71.8 mmol) and
ammonium hydroxide (25%, 13 mL) in water (25 mL) and
methanol (75 mL) were heated to 60°C for 16 hours with
stirring. The solution was diluted with water
(100 mL), the methanol evaporated and the residual
10   mixture acidified (2n HCl). The precipitated
hydantoin 21 was filtered off, washed with water and
dried. Yield: 15.2 g (90%) colorless crystals. MS
(70eV): m/z 257 (M$^+$, 22), 144 (96), 130 (100).

EXAMPLE 69

15   (See Scheme 17)

In an autoclave 21 (10 g, 38.9 mmol) in 5% aqueous
sodium hydroxide (125 mL) was heated to 150°C for
16 hours. After cooling to room temperature, the
solution was neutralized with hydrochloric acid (37%)
20   and if necessary filtered immediately to remove traces
of hydantoin 21. The solution was stirred at room
temperature for 2 hours and the precipitated amino
acid 22 filtered off, washed with water (20 mL) and
dried. 22 was isolated as pale beige crystals
25   (8.52 g, 94%). MS (70eV): m/z 232 (M$^+$, 26), 144
(100), 130 (92).

EXAMPLE 70

(See Scheme 17)

A solution of 22 (5 g, 21.5 mmol) in dry methanol
30   (375 mL) was warmed to 40°C and saturated with
hydrogen chloride (1 hour). After stirring at 40-45°C
for 5 hours and at room temperature for another
15 hours the solvent was evaporated. Water (100 mL)

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was added, the mixture neutralized with aqueous sodium carbonate and extracted with ethyl acetate (2 x 100 mL). The organic layer was washed with diluted sodium bicarbonate solution (50 mL) then with water (50 mL) and dried (Na_2SO_4). After removing the solvent the residue was chromatographed on silica gel using CH_2Cl_2/MeOH 98:2 (v/v) as eluents. 23 was isolated as beige crystals (4.0 g, 75%). MS (70eV): m/z 246 (M^+, 25), 144 (71), 130 (100).

EXAMPLE 71

(R^1 = 2-adamantyl, see Scheme 17)

The reaction of aminoester 23 with 2-adamantyl-chloroformate was done according to the conversion of 3a to 4a. 24a was isolated in 86% yield as a colorless amorphous powder. MS (70eV): m/z 424 (M^+, 42), 281 (41), 144 (100), 135 (78).

EXAMPLE 72

(R^1 = 2-adamantyl, see Scheme 17)

The hydrolysis of 24a with lithium hydroxide was done according to the hydrolysis of 4a to 5a. 25a was isolated without chromatography as a pale beige amorphous powder in quantitative yield, pure enough to be used in the next step (see Example 73) without further purification. MS (70eV): m/z 410 (M^+, 5), 130 (100).

EXAMPLE 73

(R^1 = 2-adamantyl, R^3 = R^4 = H, c = 1, see Scheme 17)
Carbamic acid, [3-(1H-indol-3-yl)-1-methyl-1-[[(2-phenylethyl)amino]carbonyl]propyl]-, tricyclo-[3.3.1.1^{3,7}]dec-2-yl ester, (±)-

The conversion of 25a with 2-phenylethylamine to 26a was done according to the conversion of 5a to 6a.

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After chromatographic separation on silica gel using CH₂Cl₂/MeOH 98:2 (v/v) 26a (Rf 0.2) was isolated in 69% yield as a colorless amorphous powder, m.p. 75-85°C. MS (70eV): m/z 513 (M⁺, 1), 370 (67), 130 (100).

In analogous manner are prepared:
(C* = configuration at the chiral C-atom of the substituted 2-phenylethylamide residue, other center is always RS)

EXAMPLE 74
(R¹ = 2-adamantyl, R³ = CH2OH, R⁴ = H, c = 1, C* = S)
Carbamic acid, [1-[[[1-(hydroxymethyl)-2-phenylethyl]-amino]carbonyl]-3-(1H-indol-3-yl)-1-methylpropyl]-, tricyclo[3.3.1.1³,⁷]dec-2-yl ester (hydroxymethyl center is S, other center is RS)
m.p. 80-90°C, CI-MS (C₄H₁₀): m/z 544 (MH+, 2), 392 (100)

EXAMPLE 75
(R¹ = (1S)-2-bornyl, R³ = R⁴ = H, c = 1
Carbamic acid, [3-(1H-indol-3-yl)-1-methyl-1-[[(2-phenylethyl)-amino]carbonyl]propyl]-, 1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl ester, [1R-[1α,2β(S), 4α]]-
m.p. 70-80°C, CI-MS (CH₄): m/z 516 (MH⁺, 2), 362 (100)

EXAMPLE 76
(R¹ = 2-adamantyl, R³ = H, R⁴ = NHCOCH = CHCO₂Me, c = 1, C* = R)
13-Oxa-2,5,8-triazatetradec-10-enoic acid, 3-[2-(1H-indol-3-yl) ethyl]-3-methyl-4,5,12-trioxo-7-phenyl-, tricyclo-[3.3.1.1³,⁷]dec-2-yl ester (TRP center is R/S mixture, other center is R, double bond E)
m.p. 117-123°C, CI-MS(C4H10): m/z 640(M-,19), 487(100)

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EXAMPLE 77

$(R^1 = 2\text{-adamantyl}, R^3 = H, R^4 = NHCOCH2CH2CO2Bz, c = 1, C^* = R)$

13-Oxa-2,5,8-triazatetradecanoic acid, 3-[2-(1H-indol-3-yl)ethyl]-3-methyl-4,9,12-trioxo-7,14-diphenyl-, tricyclo-[3.3.1.1^{3,7}]dec-2-yl ester (TRP center is R/S mixture, other center is R)

m.p. 85-95°C, CI-MS (C_4H_{10}): m/z 627 (20), 475(100), 251(44)

EXAMPLE 78

$(R^1 = (1S)\text{-}2\text{-bornyl}, R^3 = CH_2OH, R^4 = H, c = 1, C^* = S)$

Carbamic acid, [2-[[[1-(hydroxymethyl)-2-phenylethyl]amino]-carbonyl]-3-(1H-indol-3-yl)-1-methylpropyl]-, 1,7,7-trimethylbicyclo-[2.2.1]hept-2-yl ester (Bicyclo system is 1S-endo, hydroxymethyl center is S, other center is RS)

m.p. 75-85°C, CI-MS (CH_4): m/z 546 (MH^+, 82), 153 (100)

EXAMPLE 79

$(R^1 = 2\text{-adamantyl}, R^3 = H, R^4 = NHCOCH_2CH_2CO_2H, c = 1, C^* = R))$

Butanoic acid, 4-[[2-[[4-(1H-indol-3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-amino]butyl]amino]-1-phenylethyl]amino]-4-oxo- (indole center is RS, other center is R)

m.p. 115-125°C, CI-MS (C_4H_{10}): m/z 629 (MH^+, 1), 191 (28), 135 (100)

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EXAMPLE 80

(R^1 = 2-adamantyl, R^3 = H, R^4 = -NHCOCH = CHCO2H,

c = 1, C* = R)

2-Butenoic acid, 4-[2-[[2-[2-(1H-indol-3-yl)ethyl]-2-

methyl-1-oxo-3-[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)-

carbonyl]amino]propyl]amino]-1-phenylethyl]-4-oxo-

(indole center is RS, other center is R, double bond

E)

m.p. 190-200°C, CI-MS (NH$_3$): m/z 626 (M⁻, 24), 201

(60), 151 (100)

        The conversion of 26d to 26h and the conversion of

26e to 26g were done in analogy to already described

procedures.

EXAMPLE 81

(See Scheme 18)

        The method is as described for 2a (compare lit.

J. Org. Chem. 18:1440, 1447, 1953). Alkylation of

diethyl methylmalonate with gramine provided compound

28 after chromatographic separation on silica gel

using CH$_2$Cl$_2$/MeOH 98:2 (v/v) as eluents as a light red

brown syrup (yield 90%). MS (70eV): m/z 303 (M⁺, 11),

130 (100).

EXAMPLE 82

(See Scheme 18)

        To a solution of the diester 28 (31 g, 0.102 mol)

in dry ethanol (80 mL) was added a solution of

potassium hydroxide (6.5 g, 0.116 mol) in ethanol

(65 mL) dropwise at room temperature (1 hour) and

stirred for another 16 hours. The reaction mixture is

filtered and the filtrate evaporated. The residue is

suspended in water (700 mL), neutralized with

hydrochloric acid and extracted with ether (3 x

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250 mL). The ether solution was dried (Na$_2$SO$_4$), evaporated and the residue purified by chromatography on silica gel using CH$_2$Cl$_2$/MeOH 95:5 (v/v) as eluents. The monoacid 29 (Rf 0.1) was isolated as a light

5   redbrown syrup (18 g, 64%). MS (70eV): m/z 275 (M$^+$, 9), 130 (100).

EXAMPLE 83

(See Scheme 18)

To a solution of compound 29 (37 g, 0.134 mol) in

10   dry tetrahydrofuran (500 mL) at 0°C under nitrogen was added dropwise a 2 M solution of borane-methyl sulfide complex in tetrahydrofuran (100 mL, 0.2 mol) (45 min.) and stirred for 3 hours at 0°C. Then water (100 mL) was added dropwise, the mixture diluted with more

15   water (400 mL) and ethyl acetate (800 mL). The organic layer was separated, washed with water (3 x 150 mL), dried (Na$_2$SO$_4$) and evaporated. The residue was suspended in CH$_2$Cl$_2$ (100 mL), the precipitated 29 filtered off and washed with CH$_2$Cl$_2$ (30 mL). 29 was

20   isolated as colorless, sometimes slightly red crystals (26.74 g, 85%), pure enough to be used in the next step. TLC (silica gel): Rf 0.15 (toluene/tetrahydrofuran 1:1).

EXAMPLE 84

25   (See Scheme 18)

To a solution of 30 (26.6 g, 0.114 mol) in dry methanol (1.5 1) were added 4 mL sulfuric acid (95-97%) and the solution stirred at room temperature for 2 days. The solution was neutralized with sodium

30   bicarbonate solution, partially evaporated to remove the methanol, diluted with water (500 mL) and extracted with ethyl acetate (2 x 500 mL). The organic layer was washed with water (250 mL), dried

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(Na₂SO₄) and evaporated. The residue was
chromatographed on silica gel using toluene/ethyl
acetate 3:1 (v/v) as eluents. 31 was isolated as a
colorless, viscous syrup (25.7 g, 91%). MS (70eV):
5   m/z 247 (M^+, 8), 130 (100).

                        EXAMPLE 85

(See Scheme 18)
        To a solution of 31 (5.0 g, 20.2 mmol) and
pyridine (3.2 g, 40.4 mmol) in dry dichloromethane
10   (100 mL) at 0°C was added p-toluene sulphonyl chloride
(5.0 g, 26.3 mmol) in small portions. The solution
was allowed to stand for 4 days in the refrigerator at
0-5°C. The solution was washed with sodium
bicarbonate solution (2 x 50 mL), dried (Na₂SO₄) and
15   evaporated. The residue was chromatographed on silica
gel using toluene/ethyl acetate 95:5 (v/v) as eluents.
Compound 32 (Rf 0.3) was isolated as a viscous oil,
which was recrystallized from diisopropyl ether to
yield colorless crystals (6.94 g, 85%). MS (70eV):
20   m/z 401 (M^+, 8), 130 (100).

                        EXAMPLE 86

(See Scheme 18)
        Compound 32 (3.5 g, 8.13 mmol) and potassium
cyanide (0.850 g, 13.1 mmol) in dry dimethylformamide
25   (60 mL) were stirred at 110°C for 16 hours. The
solution was evaporated in vacuo and the residue
dissolved in ethyl acetate (200 mL) and water
(200 mL). The organic layer was separated, dried
(Na₂SO₄) and evaporated. The residue was purified by
30   chromatography on silica gel using toluene/ethyl
acetate 9:1 (v/v) as eluents. Compound 33 was
isolated (Rf 0.4 in toluene/ethyl acetate 4:1) as a

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colorless syrup (1 g, 45%). MS (70eV): m/z 256 (M$^+$, 8) 130 (100).

EXAMPLE 87

(R^1 = 2-adamantyl, R^3 = R^4 = H, c = 1, see scheme 18)
Carbamic acid, [3-(1H-indol-3-ylmethyl)-3-methyl-4-oxo-4-[(2-phenylethyl)amino]butyl]-, tricyclo-[3.3.1.1^{3,7}]dec-2-yl ester, (±)-

The conversion of compound 33 to compounds 37 has been done in analogy to the conversion of compounds 2 to compounds 6 (see synthetic scheme 15a). 37a has been isolated after chromatographic separation on silica gel using CH$_2$Cl$_2$/MeOH 98:2 (v/v) as eluents as a colorless amorphous solid in 52% yield, m.p. 70-80°C. MS (70eV): m/z 527 (M$^+$, 2), 130 (100).

EXAMPLE 88

(R^1 = 2-adamantyl, R^3 = -CH$_2$OH, R^4 = H, c = 1, see Scheme 18)
Carbamic acid, [4-[[1-(hydroxymethyl)-2-phenylethyl]-amino]-3-(1H-indol-3-ylmethyl)-3-methyl-4-oxobutyl]-, tricyclo-[3.3.1.1^{3,7}]dec-2-yl ester

In an analogous manner to the synthesis of 37a, compound 37b has been isolated after chromatographic separation on silica gel using CH$_2$Cl$_2$/MeOH 98:2 (v/v) as eluents as a colorless amorphous solid in 52% yield, m.p. 70-80°C. MS (70eV): m/z 527 (M$^+$, 2), 130 (100). 37b is a mixture of two diastereomers (S-configuration at the chiral center derived from (S)-(-)-phenylalaninol).

EXAMPLE 89

Ethylidene-isopropylamine (69)
Isopropylamine (85 mL, 1.0 mol) was added gradually over a period of 1 hour to acetaldehyde

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(56 mL, 1.0 mol) cooled in an ice bath. After the
addition was complete, the mixture was stirred for an
additional 20 minutes. Potassium hydroxide flakes
were added until the solution separated into
5   two layers. The organic phase was separated and
stored over crushed potassium hydroxide at 0°C. The
dried material was distilled under vacuum at room
temperature to yield the title compound (1) (51.4 g,
60%), b.p. 25-30°C/10 mm; δ H (300 M Hz; CDCl$_3$); 1.09
10   (6H, d, $\underline{J}$ 6.3 Hz, 2CH$_3$), 1.88 (3H, d, $\underline{J}$ 4.8 Hz,
CH$_3$C$\underline{H}$).

3-(Isopropyl-aminoethylidene)-indole (70)

A solution of indole (25.0 g, 0.213 mol) in
glacial acetic acid (150 mL) was cooled in an ice bath
15   and ethylidene-isopropylamine (69) (17.3 g, 0.203 mol)
in toluene (50 mL) added dropwise, with stirring over
a period of 1 hour. The resulting mixture was kept at
0°C for 5 days. After this period the mixture was
poured onto an ice-ether mixture. The ether layer was
20   separated and extracted with 1N potassium hydrogen
sulphate (2 x 100 mL). The combined aqueous phase was
washed with ether (2 x 50 mL), then made basic with
10N sodium hydroxide (keeping the temperature below
25°C). The alkaline solution was extracted with ether
25   (4 x 250 mL). The organic phase was dried (MgSO$_4$) and
evaporated to dryness to give the title compound (2)
(24.6 g, 60%), m.p. 107-112°C (lit.,[1] 108-114°C); υ_{max}
(film) 3 479 cm^{-1} (indole NH); δ H (300 M Hz, CDCl$_3$),
1.01 (3H, d, $\underline{J}$ 6 Hz, CH$_3$), 1.09 (3H, d, $\underline{J}$ 6 Hz, CH$_3$),
30   1.52 (1.52 (3H, d, $\underline{J}$ 6.6 Hz, CH$_3$), 2.88 (1H, septet, $\underline{J}$
6 Hz, C$\underline{H}$(CH$_3$), 4.27 (1H, q, $\underline{J}$ 6.6 Hz, indC$\underline{H}$)CH$_3$),
7.08-.25 (4H, m), 7.35 (1H, s, $\underline{J}$ 8 Hz, NH), 7.71 (1H,
d, $\underline{J}$ 8 Hz, indole 4-H), 8.21 (1H, brs, indole NH).

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Dibenzylacetamidomalonate (71)

Diethylacetamidomalbonate (9.1 g, 42 mmol)
[Aldrich] in benzyl alcohol (26 mL, 0.25 mmol) was
heated in an oil bath at 200°C. A slow stream of
nitrogen was bubbled through the solution and the
ethanol distilled out. After 4 hours the reaction
mixture was cooled to room temperature and the excess
benzyl alcohol removed *in vacuo* with the oil bath
temperature being slowly raised to 185-190°C, at which
point distillation became very slow. The solution was
cooled to room temperature and the resulting
precipitate recrystallized from isopropanol to yield
the title compound (71) (12.2 g, 85%); m.p. 111-112°C
(lit.,[1] 110-113°C); v_{max} (film) 1752, 1734 (ester C =
0), 1651 (amide C = 0), 740 and 694 cm^{-1} (mono
substituted pH); δ H (300 M Hz, CDCl$_3$), 2.05 (3H, s,
C$\underline{H}_3$CO), 5.17 (2H, s, CH$_2$Ph), 5.18 (2H, s, CH$_2$Ph), 5.29
(1H, d, $\underline{J}$ 7 Hz, C$\underline{H}$CO$_2$CH$_2$Ph)$_2$), 6.53 (1H, brd, $\underline{J}$ 6 Hz,
NH), 7.27 (10H, m, 2Ph), δ c (75.5 M Hz, CDCl$_3$), 22.5,
56.5, 68, 128.5, 134.5, 166, 170.

Dibenzyl (3-indolylethylidene)acetamidomalonate (72)

The amine (70) (5.41 g, 26.7 mmol), diester (71)
(9.12 g, 26.7 mmol) and sodium methoxide (38 mg,
0.70 mmol) were heated in toluene (30 mL) at 85-95°C
(bath temperature) while a slow stream of nitrogen was
bubbled through the solution. The reaction mixture
was kept at this temperature for 5 hours, then cooled
to -40°C (freezer). The crude product was filtered
and recrystallized from isopropanol to yield the title
compound (72) (8.22 g, 64%), m.p. 162-163°C (Pr^{i}OH)
(lit.,[1] 161-163°C); v_{max} 1737 (ester C = 0), 1672
(amide C = 0), 743 and 697 cm^{-1} (monosubstituted Ph);
δ H (300 M Hz, CDCl$_3$), 1.57 (3H, d, $\underline{J}$ 7 Hz, CH$_3$), 1.97
(3H, s, C$\underline{H}_3$CO), 4.32 (1H, q, $\underline{J}$ 7 Hz, C$\underline{H}$ CH$_3$)), 4.72

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(1H, d, J 12 Hz, one of CH$_2$Ph), 4.89 (1H, d, J 12 Hz, one of CH$_2$OH), 5.08 (1H, d, J 12 Hz, one of CH$_2$Ph), 5.20 (1H, d, J 12 Hz, one of Ch$_2$Ph), 6.56 (1H, s, NH), 6.86 (1H, d, J 2 Hz, indole 2-H), 7.02-7.33 (13H, m, indole + 2Ph), 7.54 (1H, J 8 Hz, indole 4-H), 8.15 (1H, br s, indole N$\underline{H}$), δ C (75.5 M Hz, CDCl$_3$), 18, 23, 37, 68, 70, 111.5, 115, 119.5, 122, 122.5, 127, 128, 134.5, 136, 167, 168, 169.5.

(3-Indolylethylidene)acetamidomalonic acid (73)

The diester (72) (930 mg, 1.92 mmol), palladium hydroxide on carbon (Pearlman's catalyst) (125 mg) and 95% ethanol (110 mL) were placed in a Parr hydrogenation vessel and subjected to a hydrogen pressure of 45 psi at 25°C for 3 hours (until the uptake of hydrogen ceased). The reaction mixture was filtered through Celite to remove the catalyst, then evaporated to dryness to give the title compound (73) (576 mg, 99%) which was used without further purification. δ H (300 M Hz; D$_2$O), 1.55 (3H, d, J 7 Hz, CH$_3$), 1.99 (3H, s, C$\underline{H}_3$CO), 4.09 (1H, brd, J 7 Hz, C$\underline{H}$,(CH$_3$), 7.12-7.24 (3H, m), 7.49 (1H, d, J 8 Hz, indole 7-H), 7.71 (1H, d, J 8 Hz, indole 4-H).

2-Acetamido-3-(3-indolyl)butanoic acid (74)

The malonic acid (73) (5.48 g, 18.0 mmol) was refluxed in pyridine/water (1:1) (20 mL) until no diacid remained (S$_i$O$_2$:EtOH-EtOAc (1:1) + 1% AcOH; rf 0.26). The reaction mixture was cooled, diluted with water (50 mL), and acidified with 10% sulphuric acid (50 mL). The resulting solution was left at 0°C overnight to crystallize. The brown solid was filtered off and dried to yield 2-acetamido-3-(3-indolyl)butanoic acid isomer A (74A) (1.30 g, 28%); δ H (300 M Hz; d$_6$-DMSO), 1.32 (3H, J 9 Hz, CH$_3$),

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1.84 (3H, s, CHH₃CO), 3.46-3.55 (1H, m, indCH(CH₃)-),
4.58-4.67 (1H, m, CH(COOH)NHAc), 6.93-7.19 (3H, m),
7.34 (1H, d, J 8 Hz, amide NH), 7.54 (1H, J 8 Hz,
indole 7-H), 8.04 (1H, d, J 9 Hz, indole-4H), 10.81
5   (1H brs, indole NH), ca 12.4 (vbrs, CO₂H). The
filtrate was extracted with ethyl acetate
(4 x 100 mL). The ethyl acetate extracts were
combined and washed with water (2 x 50 mL) then
extracted with 10% sodium hydrogen carbonate
10   (2 x 100 mL). The sodium hydrogen carbonate extract
was acidified with 4N sulphuric acid then extracted
with ethyl acetate (2 x 75 mL). The ethyl acetate
solution was washed with water (2 x 25 mL) then
evaporated to dryness to give a beige foam,
15   2-acetamido-3-(3-indolyl)butanoic acid isomer B (74B)
(2.17 g, 46%); δ H (300 M Hz, d₆-DMSO), 1.32 (3H, d, J
7 Hz, CH₃), 1.84 (3H, s, CH₃CO), 3.50 (1H, M, ind
CH(CH₃)-), 4.66 (1H, m, CH(COOH)NHAc), 6.93-719 (3H,
m), 7.34 (1H, d, J 8 Hz, amide NH), 7.63 (1H, d, J
20   8 Hz, indole 7-H), 7.84 (1H, d, J 9 Hz, indole 4-H),
10.83 (1H, s, indole NH), ca 12.5 (vbrs, CO₂H).

Deacetylation of acids (74A) and (74B)

    The acids (74A) and (74B) were deacetylated
separately by the same procedure. Nitrogen was
25   bubbled through a mixture of acid (74B) (3.96 g,
15.2 mmol) in 4N sulphuric acid (25 mL) for
30 minutes, then the mixture was refluxed until all
the solid dissolved. The solution was cooled to room
temperature and neutralized to pH 8 with 0.4N barium
30   hydroxide. The barium salts were precipitated with
solid carbon dioxide, the mixture heated to boiling
point and filtered hot. The solvent was removed in
vacuo and the crude product purified by reverse phase
column chromatography [methanol-water (1:6) as eluant]

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to give 2-amino-3-(3-indolyl)butanoic acid (75)
(2.34 g, 71%) in a ratio of 1:3 (75A:75B),
m.p. 198-212°C (lit.[1], 218-225°C dec); isomer A δ H
(300 M Hz, D_2O), 1.33 (3H, d, $\underline{J}$ 7 Hz, CH_3), 3.66-3.75
5   (2H, m, indC$\underline{H}$(CH_3)- + C$\underline{H}$(Co_2H)NH_2), 7.20-7.34 (2H, m),
7.57 (1H, d, $\underline{J}$ 8 Hz, indole 7-H), 7.87 (1H, d, $\underline{J}$ 8 Hz,
indole 4-H), isomer B, δ H (300 M Hz, D_2O), 1.37 (3H,
d, $\underline{J}$ 7 Hz, CH_3), 3.30-3.42 (2H, m, ind C$\underline{H}$(CH_2)- +
-C$\underline{H}$(CO_2H)NH_2), 7.09-7.24 (3H, m), 7.48 (1H, d, $\underline{J}$ 8 Hz,
10   indole 7-H), 7.73 91H, d, $\underline{J}$ 8 Hz, indole 4-H).

2-Adamantylchloroformate

A solution of 2-adamantanol (10.1 g, 66.5 mmol) in
dichloromethane (200 mL) was cooled in an ice bath.
Bis(trichloromethyl)carbonate (triphosgene) (7.55 g,
15   25.4 mmol) was added followed by dropwise addition of
pyridine (6.2 mL, 77 mmol) at such a rate that the
temperature remained below 20°C. After a further
10 minutes the mixture was warmed to room temperature
and stirred for a further 2.5 hours. The
20   dichloromethane was removed $\underline{in\ vacuo}$ without heating
and the residue slurried with ethyl acetate (50 mL).
The pyridinium hydrochloride was filtered off and the
filtrate evaporated to dryness without heating to
yield 2-adamantylchloroformate (76) (13.7 g, 96%); δ H
25   (300 M Hz, $CDCl_3$, 1.48-2.32 (14H, m, adamantyl), 5.01
(1H, t, J 3 Hz, adamantyl 2-H); (lit.,[2] δ H (CCl_4)
1.3-2.4 (14H, m), 4.95 (1H, s).

2-(2-Adamantyloxycarbonyl)amino-3-(3-indolyl)butanoic acid (77)

30   Percent amino acid (75) (449 mg, 2.29 mmol) in 1N
sodium hydroxide (2.29 mL) was added to sodium
hydrogen carbonate (211 mg, 2.5 mmol). This mixture
was cooled to 0°C (ice bath), dioxan. (2.29 mL) was

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added, followed by dropwise addition with stirring of
a solution of the chloroformate (76) (742 mg,
34.46 mmol) in dioxan (2.29 mL). When all the amino
acid had gone (TLC SiO$_2$:4% methanol in
5   dichloromethane), the dioxan was removed _in vacuo_ and
the residue partitioned between 10% citric acid and
ethyl acetate. The aqueous phase was extracted
further with ethyl acetate. The organic extracts were
combined, dried (MgSO$_4$), and evaporated to dryness.
10   The crude acid was purified by column chromatography
on normal silica [hexane:ethyl acetate (3:20 + 0.5%
acetic acid as eluant] to give 2-(2-adamantyloxy-
carbonyl)amino-3-(3-indolyl) butanoic acid (77)
(570 mg, 63%); δ H (300 M Hz, d$_6$-DMSO), 1.34 (3H, d, _J_
15   8Jz. CH$_3$), 1.68-2.00 (14H, m, adamantyl), 3.40-3.53
(1H, m, indCH(CH$_3$)), 4.36 (1H, brt, CH(CO$_2$H)), 4.59
(1H, s, adamantyl 2-H), 6.73 (1H, d, _J_ 9 Hz, urethane
NH), 6.96 (1H, t, _J_ 7 Hz, indole 5-H), 7.06m (1H, t, _J_
7 Hz, indole 6-H), 7.17 (1H, brs, indole 2-H), 7.33
20   (1H, d, _J_ 8 Hz, indole 7-H), 7.60 (1H, d, _J_ 8 Hz,
indole 4-H), 10.83 (1H, s, indole NH)m, ca 12.6 (vbrs,
CO$_2$H).

2-Adamantyloxycarbonyl-D,L-ß-methyl-D,L-tryptophan-L-
phenylalaninol (78)
25   The carboxylic acid (77) (288 mg, 0.726 mmol),
N,N'-dicyclohexyl-carbodiimide (DCCI) (173 mg,
0.838 mmol) and 1-hydroxybenzotriazole (HOBT) 9121 mg,
0.895 mmol) in ethyl acetate (5 mL) were stirred for
1 hour at 0°C. Dimethylaminopyridine (DMAP) (23 mg,
30   0.19 mmol) and phenylalaninol (163 mg, 1.08 mmol) were
added, and the mixture stirred for a further 2 hours
at 0°C then for 48 hours at room temperature. The
mixture was filtered and the filtrate washed with 5%
citric acid (2 x 10 mL), saturated sodium hydrogen

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carbonate (10 mL), 5% citric acid again (10 mL), and
brine (10 mL), dried (MgSO$_4$), and evaporated to
dryness. The crude product was purified by column
chromatography on normal silica [ethyl acetate:hexane
5   (1:1) as eluant] to yield 2-adamantyloxycarbonyl-D,L-
ß-methyl-D,L-tryptophan-L-phenylalaninol (78) (45 mg,
12%); m.p. 99-101°C (Found: C, 71.7; H, 7.65; N, 7.4.
C$_{32}$H$_{39}$N$_3$O$_4$·0.5H$_2$O requires C, 71.35; H, 7.5; N, 7.8%);
v_{max} (film) 3360 (OH), 1 695 (urethane C = O), 1658
10   (amide C = O), 746 and 702 cm^{-1} (monosubstituted Ph);
δH (300 M Hz, CDCl$_3$), 1.42 (3H, d, $\underline{J}$ 7 Hz, CH$_3$),
1.45-2.10 (14H, m, adamantyl), 2.20 (1H, brs, OH),
2.43-2.69 (2H, m, CH$_2$Ph), 2.84 (1H, brs, ind C$\underline{H}$(CH$_3$-),
3.39 (2H, br, m, CH$_2$OH), 3.86 (1H, brs,
15   C$\underline{H}$(CH$_2$Ph)CH$_2$OH), 4.49 (1H, m, C$\underline{H}$(NMR)(CONH-), 4.79
(1H, s, adamantyl 2-H), 5.49 (1H, brs, urethane NH),
6.87 (1H, brs, amide NH), 6.95-7.38 (9H, m, indole +
Ph), 7.69 (1H, d, $\underline{J}$ 7 Hz, indole 4-H), 8.26 (1H, s,
indole NH); m/z (FAB) 530 (M$^+$ + 1), 257, 232, 217,
20   181, 144, 126 (100%), 109.

EXAMPLE 90
N-[D-3-(1H-indol-3-ylmethyl)-3-methyl-N-[(tricyclo
[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-ß-alanyl]-L-2-
phenylglycine, AdOC-((D)-3-(1H-indol-3-ylmethyl)bAla-
25   (L)-2-phenyl)Gly

Step 1. Synthesis of 2AdocαMeRTrp CHN$_2$ (diazoketone).
A solution of N-methylmorpholine (253 mg,
2.50 mmol) and 2ADOCαMe-$\underline{R}$-TrpOH (990 mg, 2.50 mmol) in
anhydrous THF (20 mL) at 0°C was treated dropwise with
30   a solution of iso-butyl chloroformate (340 mg,
2.50 mmol) in anhydrous THF (10 mL) and left stirring
for 20 minutes). The reaction mixture was then
filtered and a solution of diazomethane (6 mmol) in

ether was added to the filtrate. This was then
allowed to warm to room temperature and left 12 hours.
Excess diazomethane was quenched with AcOH (1 mL) and
the mixture evaporated to dryness in vacuo. The
residue was then separated by silica gel
chromatography using n-hexane:EtOAC (4:1 then 3:1) as
eluants to give the diazoketone (Scheme 19, No. 2) as
yellow crystals. M.p. 182.2-182.7°C (MeOH);
$[\alpha]_D^{20}$ = +64° (c = 0.5, MeOH); IR (film) 3400-3200,
2913, 2854, 2106, 1693 and 1352 cm^{-1}; NMR (CDCl$_3$)δ 1.49
(3H, s), 1.50-1.60 (2H, m), 1.70-2.05 (12H, m), 3.30-
3.40 (2H, br s), 4.86 (1H, s), 5.20-5.40 (1H, br s),
5.56 (1H, s), 6.95 (1H, d, J 2 Hz), 7.08 (1H, t, J
7 Hz), 7.16 (1H, t, J 7 Hz), 7.33 (1H, d, J 8 Hz),
7.55 (1H, d, J 8 Hz), 8.50 (1H, s); MS 71e (FAB) 421.3
(11), 393.2 (54), 351.2 (9), 307.2 (22) and 259.1
(100);
Analysis for C$_{24}$H$_{28}$N$_4$O$_3$:
Calc.: C, 68.55; H, 6.71; N, 13.32%
Found: C, 68.51; H, 6.73; N, 13.26%

Phenylmethyl (R)-ß-methyl-ß-[[(tricyclo[3.3.1.1^{3,7}]dec-
2-yloxy)carbonyl]amino]-1H-indole-3-butanoic acid

Step 2. Synthesis of the above compound (Scheme 19,
No. 3)
      A solution of the diazoketone (as prepared in
Step 1) (4-20 g, 10.0 mmol) in benzyl alcohol (30 mL)
was treated with a solution of silver benzoate (6 mL
of a solution containing 1 g silver benzoate in 10 mL
Et$_3$N) at room temperature. This was stirred for
4 hours, treated with activated charcoal and filtered
through gypsum. The benzyl alcohol was removed in
vacuo and the residue separated by silica gel
chromatography using CH$_2$Cl$_2$ as eluant to give the

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benzyl ester (Scheme I, No. 2) as a glass (3.3 g,
66%); m.p. 47-52°C; $[\alpha]_D^{20}$ = +17.6° (c = 1, MeOH); IR
(film) 3500-3200, 2908, 2855, 1750-1680 cm^{-1}; NMR
(CDCl$_3$) δ 1.39 (3H, s), 1.51 (1H, s), 1.54 (1H, s),
5   1.70-2.05 (12H, m), 2.68 (1H, o, J 14.3 Hz), 2.97 (1H,
d, J 14.3 Hz), 5.10 (3H, s), 6.99 (1H, d, J 2.3 Hz),
7.08 (1H, t, J 7 Hz), 7.16 (1H, b, J 7 Hz), 7.30-7.35
(6H, m), 7.58 (1H, d, J 7.8 Hz), 8.05 (1H, s); MS M/e
(FAB) 501.3 (28), 370.3 (24), 326.3 (29), 306.2 (32)
10   and 135.2 (100);
Analysis for C$_{31}$H$_{36}$N$_2$O$_4$:
Calc.: C, 74.37; H, 7.25; N, 5.60%
Found: C, 74.44; H, 7.20; N, 5.75%

(R)-ß-methyl-ß-[[(tricyclo[3.3.1.1^{3,7}]dec-2-
15   yloxy)carbonyl]amino]-1H-indole-3-butanoic acid, AdOC-
(α-Me)DTrp

Step 3. Synthesis of the above compound (Scheme 19
No. 4)
     A solution of the benzyl ester (as prepared in
20   Step 2) 1.0 g, 2 mmol) in absolute ethanol (100 mL)
was treated with 10% palladium on carbon (100 mg, 10%
w/w) and the resulting suspension subjected to an
atmosphere of hydrogen at 50 psi for 4 hours with
agitation at temperature of 30°C. This reaction
25   mixture was then filtered through gypsum and the
solvent removed in vacuo. The residue was column
chromatographed over reverse phase silica using
MeOH:H$_2$O (3:1) as eluant and the solid product
recrystallized from chloroform to give the acid as a
30   white solid (700 mg, 85%), m.p. 198-201°C (CHCl$_3$);
$[\alpha]_D^{20}$ = +20° (c = 1, MeOH); IR (film) 3500-3300, 2912,
2856, 1704 and 734 cm^{-1}; NMR (CDCl$_3$) δ 1.41 (3H, s),
1.53 (1H, s), 1.57 (1H, s), 1.70-1.85 (9H, m),

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1.95-2.10 (4H, m), 2.69 (1H, d, J 14.3 Hz), 3.05 (1H,
d, J 14.3 Hz), 3.21 (1H, d, J 14.3 Hz), 3.32 (1H, d, J
14.4 Hz), 4.86 (1H, s), 5.10-5.30 (1H, br s), 7.04
(1H, d, J 2.2 Hz), 7.07-7.20 (2H, m), 7.;35 (1H, d, J
8 Hz), 7.60 (1H, d, J 7.7 Hz), 8.16 (1H, s); MS M/e
(FAB) 411.5 (9) and 217.2 (100);

Analysis for $C_{24}H_{30}N_4O_4$:

Calc.:   70.22; H, 7.37; N, 6.82%

Found: 70.03; H, 7.38; N, 6.78%

Methyl N-[D-3-(1H-indol-3-ylmethyl)-3-methyl-N-
[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-ß-alanyl]-
L-2-phenylglycine

Step 4.   Synthesis of the above compound (Scheme 19
No. 5)

A stirred solution of the acid (as prepared in
Step 3) (500 mg, 1.20 mmol) and pentafluorophenol
(224 mg, 1.20 mmol) in EtOAC (50 mL) at 0°C was
treated with N, N'-dicyclohexylcarbodiimide (263 mg,
1.30 mmol). This mixture was stirred 18 hours at 0°C,
filtered and S-phenyl glycine methyl/ester (303 mg,
1.50 mmol) added to the filtrate. This reaction
mixture was left at room temperature for 48 hours,
washed with 1M citric acid solution (2 x 20 mL),
saturated NaHCO$_3$ solution (2 x 20 mL) and H$_2$O
(2 x 20 m). The dried (MgSO$_4$) organic phase was
evaporated to dryness in vacuo and the residue
separated by reverse phase silica gel chromatography
using MeCH:H$_2$O (3:1) as eluant to give the ester
(Scheme 1 No. 5) as a noncrystalline solid (600 mg,
90%). M.p. 72-82°C; $[\alpha]_D^{22}$ = +55.3^6 (c = 1, MeOH); IR
(film) 3500-3200, 2916, 2856, 1743, 1694, 1657 and
1504 cm^{-1}; NMR (CDCl$_3$) δ 1.35 (3H, s), 1.40-1.55 (2H,
m), 1.70-2.05 (12H, m), 2.54 (1H, d, J 13.3 Hz), 3.04-

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3.15 (2H, m), 3.31 (1H, d, J 14.2 Hz), 3.71 (3H, s),
4.71 (1H, s), 5.09 (1H, s), 5.48 (1H, d, J 6.6 Hz),
6.85 (1H, d, J 6.1 Hz), 7.04 (1H, d, J 2 Hz), 7.08
(1H, g, J 7 Hz), 7.17 (1H, g, J 7 Hz), 7.30-7.40 (6H,
m), 7.59 (1H, d, J 7.6 Hz), 8.14 (1H, s); MS M/e
(FAB), 558.3 (12), 383 (11), 198.1 (34), 170.1 (27)
and 135.1 (100);

Analysis for $C_{33}H_{39}N_3O_5$:

Calc.: C, 71.07, H, 7.05; N, 7.53%

Found: C, 71.31; H, 7.30; N, 7.28%

Glycine, N-[D-3-(1H-indol-3-ylmethyl)-3-methyl-N-
[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-ß-alanyl]-
L-2-phenyl-AdOC-((D)-3-(1H-indol-3-ylmethyl)bAla-((L)-
2-phenyl)Gly·
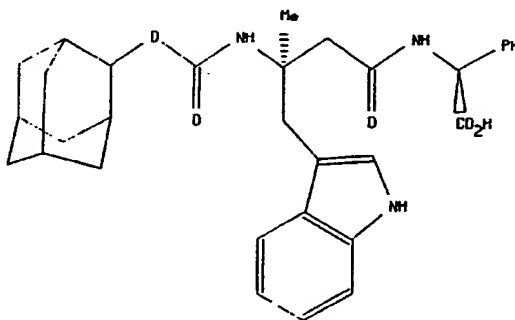
     A stirred solution of the ester (as prepared in
Step 4) (399 mg, 0.70 mmol) in THF (20 mL) was treated
with a solution of ClOH (30 mg,   mmol) in H_2O (5 mL)
at room temperature. After 2 hours the mixture was
made acidic to pH paper by adding 1M HCl solution.
The solvent was then removed under vacuum and the
residue separated by reverse phase silica gel
chromatography using MeOH:H_2O (3:1) as eluant to give
the product (Example 90) as a noncrystalline solid
(200 mg, 53%); m.p. 120-125°C; $[\alpha]_D^{20}$ = +49.2°

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(c = 0.5, MeOH); IR (film) 3450-3250, 2916, 2856,
1750-1600, 1510 and 1256 cm^{-1}; NMR (CDCl$_3$) δ 1.34 (3H,
s), 1.50-1.55 (2H, m), 1.60-200 (12H, m), 2.58 (1H, d,
J 12.7 Hz), 3.00-3.25 (3H, m), 2.50-4.00 (1H, br),
5   4.60-4.75 (1H, br s), 4.90-5.20 (1H, br s), 5.54 (1H,
d, J 6.5 Hz), 7.00-7.60 (10H, m), 7.58 (1H, d, J
7.9 Hz), 8.14 (1H, s);
Analysis for C$_{32}$H$_{37}$N$_3$O$_5$·O$_3$·H$_2$O:
Calc.: C, 70.00; H, 6.90; N, 7.65%
10 Found: C, 69.97; H, 6.85; N, 7.64%

EXAMPLE 91
[R-(R*,S)]-α-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2-
[[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]amino]
propyl]amino]benzeneacetic acid, [R-(R*,S*)]-AdOC-(α-
15 Me)DTrp-L-phenylglycine (See Scheme 20)
Step 1. Synthesis of oxazolone (R)(4-(1H-indol-3-
ylmethyl)-4-methyl-2-(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)-
5(4H)-oxazolone) (No. 2, Scheme 20)
     A solution of AdOCαMe-R-TrpOH (1.0 g, 2.5 mmol)
20 and N,N'dicyclohexylcarbodiimide (0.52 g, 2.5 mmol) in
anhydrous DMF (5 mL) was stirred for 1 hour at room
temperature. This mixture was then filtered and the
filtrate evaporated to dryness in vacuo. The residue
was chromatographed on silica gel using hexane:EtOAC
25 (6:1) as eluant to give the oxazoline (2, Scheme 20)
as white crystalline needles (850 mg, 90%).
M.p. 150.5-150.9°C (hexane); [α]$_D^{20}$ = +9.0° (c = 1,
MeOH); IR (film), 2910, 2857, 1823, 1681 and
1399 cm^{-1}; NMR (CDCl$_3$) δ 1.10-1.20 (1H, m), 1.30 (15H,
30 m), 2.04 (1H, s), 3.20 (1H, d, J 14.5 Hz), 3.25 (1H, J
14.5 Hz), 4.72 (1H, t, J 3.5 Hz), 6.99 (1H, d, J
2.4 Hz), 7.07 (1H, dt, J 7.1 Hz), 7.14 (1H, dt, J 7.5
and 1 Hz), 7.29 (1H, d, J 7.3 Hz), 7.64 (1H, d, J

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7.6 Hz), 8.02 (1H, s); MS $\underline{M}/\underline{e}$ (CI) 379.2 (52), 178.3
(47), 163.3 (61), 135.2 (74) and 130.2 (100);
Analysis for $C_{23}H_{26}N_2O_3$:
Calc.: C, 72.99; H, 6.92; N. 7.40%

5   Found: C, 72.88; H, 6,96; N, 7.37%

Step 2

        A suspension of $\underline{S}$-phenylglycine (42 mg,
0.28 mmol), NaHCO$_3$ (23 mg, 0.28 mmol) and the
oxazolone (Scheme 20, No. $\underline{2}$) (100 mg, 0.26 mmol) in

10   DMF:H$_2$O (1:1) (10 mL) was stirred at room temperature
for 18 hours. The solvent was then removed $\underline{in\ vacuo}$
and the residue suspended between EtOAC (20 mL) and 1$\underline{M}$
citric acid solution (20 mL). The aqueous phase was
partitioned and extracted with EtOAC (2 x 20 mL) and

15   the combined organic phases washed with H$_2$O
(3 x 10 mL), dried over MgSO$_4$ and the solvent removed
$\underline{in\ vacuo}$. The residue was then subject to silica gel
chromatography using 3% MeOH in CH$_2$Cl$_2$ then 5% MeOH,
0.5% H$_2$OH in CH$_2$Cl$_2$ to give the product (Example 91) as

20   a noncrystalline solid (106 mg, 77%). M.p. 138-143°C;
$[\alpha]_D^{24}$ = +82° ($\underline{c}$ = 1, MeOH); IR (film) 3500-3200, 2913,
2855, 1696, 1666 and 1499 cm^{-1}; NMR (CDCl$_3$) δ 1.40-1.50
(2H, m), 1.56 (3H, s), 160-1.95 (12H, m), 3.26 (1H, d,
$\underline{J}$ 14.6 Hz), 3.40 (1H, d, $\underline{J}$ 14.6 Hz), 4.73 (1H, s),

25   5.68 (1h, d; $\underline{J}$ 6.8 Hz), 5.40-5.80 (1H, br), 6.90 (1H,
s), 7.00-7.15 (2H, m), 7.20-7.30 (6H, s), 7.35 (1H, ·d,
$\underline{J}$ 6.8 Hz), 7.53 (1H, d, $\underline{J}$ 7.5 Hz), 8.41 (1H, s); MS
$\underline{M}/\underline{e}$ (FAB) 530.5 (13), 217.2 (38);
Analysis for $C_{31}H_{35}N_3O_5O2H_2O$:

30   Calc.: C, 69.83; H, 6.69; N, 7.88%
        Found: C, 69.85; H, 6.66; N, 7.74%

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EXAMPLE 92

<u>Tricyclo[3.3.1.1^{3,7}]dec-2-yl(r)-[2-[2-phenylethyl)-
amino]-1-(1H-indol-3-yl)-1-methylethyl]carbamate (See
Scheme 21)</u>

5   To a solution of lithium borohydride (4 mL, 2M
solution, 8 mmol) in dry THF under a nitrogen
atmosphere was added a solution of
chlorotrimethylsilane (1.75 g, 16.0 mmol) in dry THF
(5 mL). A white precipitate (of lithium chloride) was
10   observed. After 2 minutes a solution of (18) (1 g,
2 mmol) in THF (15 mL) was added slowly (over
3-4 minute period) and the reaction mixture was
stirred for 20 hours at ambient temperature. The
reaction was treated cautiously with MeOH (5 mL) and
15   the volatiles were removed <u>in vacuo</u> at 40°C. The
residue was purified by silica gel chromatography
using hexane:ethyl acetate (80:20) as eluant to give
(19) (0.14 g, 14%) as a colorless oil, and recovered
(18) (0.52 g; yield of (19) based on recovered
20   starting material 30%). The amine (19) (0.14 g,
0.28 mmol) was taken dissolved up in MeOH (5 mL) and
treated with 4-toluenesulfonic acid hydrate (0.054 g,
0.28 mmol). The solution was evaporated to leave a
white solid. [α]$_D$ = +22° (c = 0.25, MeOH) IR (film)
25   2928 and 1708 (c = urethane). NMR (DMSO-d$_6$) δ 1.2
(3μ, s, CH$_3$), 1.4-2.1 (14H, m, adamantyl), 2.3 (3H, s,
CH$_3$Ph), 2.9-3.7 (8H, m, 4 x CH$_2$), 4.7 (1H, br s,
adamantyl H-2), 6.9-7.6 (15H, m, aromatics), 8.3 (1H,
br, one of NH$_2^+$), 8.5 (1H, br, one of NH$_2^+$), 11.0 (1H,
30   s, indole NH); MS <u>M/e</u> (FAB) 486 (m+ + H) (100), 136
(52);
Analysis for C$_{31}$H$_{39}$N$_3$O$_2$·C$_7$H$_8$SO$_3$·0.75H$_2$O:
Calc.: C, 67.98; H, 7.28; N, 6.26
Found: C, 67.96; H, 7.31; N, 600. M.p. 90-93°C

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Ethyl[R-(R*,S*)]-4-[[2-phenylethyl]-[3-(1H-indol-3-
yl)-2-methyl-2-[[(tricyclo[3.3.1.1^{3,7}]dec-2-
yloxy)carbonyl]amino]propyl]amino]-4-oxo-butanoate
(19b, Scheme 21).

5   Prepared by a similar method to compound (19a).
Recovered a white solid 0.102 g (81%); $[\alpha]_D^{21}$ = +26°
(c = 0.5, CHCl$_3$); IR (film) 2905, 2853, 1732, 1711,
1634 cm^{-1}; NMR (CDCl$_3$) δ 1.2 (6H, m), 1.3-2.1 (14H, m),
2.6 (4H, br s), 2.9 (2H, m), 3.0 (1H, d, $\underline{J}$ 14 Hz),
10   3.3-3.8 (4H, m), 4.0-4.2 (3H, m), 4.8 (1H, br s), 5.3
(1H, br), 6.9-7.6 (10H, m), 8.1 (1H, br s); MS $\underline{M}/\underline{e}$
(FAB) 614 (36) (M$^+$ + H), 483 (100), 419 (24);
Analysis for C$_{37}$H$_{47}$N$_3$O$_5$:
Calc.: C, 72.40; H, 7.72; N, 6.85%
15   Found: C, 72.11; H, 7.87; N, 6.16%. M.p. 67-70°C

Tricyclo[3.3.1.1^{3,7}]dec-2-yl[R-(R*,S*)]-[2-[acetyl[2-
phenylethyl]amino]-1-(1H-indol-3-ylmethyl)-1-
methylethyl]carbamate (19a in Scheme 21)

     To a solution of (19) (0.1 g, 0.2 mmol) in
20   dichloromethane (20 mL) at 0°C was added acetyl
chloride (0.3 mL, 4 mmol), followed by triethylamine
(4 drops). Stirring was continued at 0°C for
20 minutes, then the reaction mixture was dissolved in
ethyl acetate (50 mL), washed (HCl aq, H$_2$O, NaHCO$_3$
25   ag), dried (MgSO$_4$) and evaporated to dryness. The
residue was purified by column chromatography using
hexane-ethyl acetate eluent to give an off-white solid
(0.092 g, 85%). $[\alpha]_D^{21}$ = +24° (c = 0.25, CHCL$_3$), IR
(film) 2909, 2855, 1709, 1610 cm^{-1}; NMR (CDCl$_3$) δ 1-3
30   (3H, s), 1.4-2.1 (17H, m), 2.8 (2H, m), 3.1 (1H, d, $\underline{J}$
14 Hz), 3.3-3.7 (4H, m), 4.0 (1H, d, $\underline{J}$ 14 Hz), 4.8
(1H, s), 5.5 (1H, br s), 6.9-7.7 (10H, m), 8.1 (1H, br
s); MS $\underline{M}/\underline{e}$ (FAB), 528 (45) (M$^+$ + H), 397 (100), 333
(27).

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4-[[3-(1H-indol-3-yl)-2-methyl-2-[[(tricyclo[3.3.1.1^{3,7}]-dec-2-yloxy)carbonyl]amino]propyl](2-phenylethyl)amino]-4-oxobutanoic acid (19d, Scheme 21).

5

To a stirred solution of (19b) (0.04 g, 0.06 mmol) in THF (5 mL) was added methanol (5 mL), water (5 mL) and lithium hydroxide monohydrate (0.1 g, 2.4 mmol). The reaction mixture was stirred for 40 minutes at ambient temperature, then acidified (2NHCl aq, 50 mL) and the products extracted into ethyl acetate (50 mL).

10

The organic phase was dried with magnesium sulphate and evaporated <u>in vacuo</u> (40°C). The oily residue was purified by column chromatography using dichloromethane/methanol (9:1) as eluent. Recovered 0.031 g (81%) of a white solid; IR (film) 340 (br), 2912, 2852, 1714, 1700, 1635 cm^{-1}; NMR (MeOH-d$_4$) δ 1.1-2.2 (17H, m, CH$_3$ + adamantane), 2.6-3.2 (6H, m, 3 x CH$_2$), 3.4-4.1 (6H, m, 3 x CH$_2$), 4.8 (1H, br, adamantane H-2), 7.0-7.6 (10H, m, aromatics); [α]$_D$ +4° (MeOH, C = 0.2, 22°C); FAB MS 586 (51) m$^+$ + H), 455 (100), 391 (24)%

15

20

Analysis of C$_{35}$H$_{43}$N$_3$O$_5$·0.25 H$_2$O:
Calc.: C, 71.22, H, 7.43; N, 7.12
Found: C, 71.24; H, 7.46; N, 6.87%, m.p. 99-96°C

EXAMPLE 93

Tricyclo[3.3.1.1^{3,7}]dec-2-yl [R-(R*,S*)]-[2-[[1-(hydroxymethyl)-2-phenylethyl]amino]-1-(1H-indol-3-ylmethyl)-2-oxoethyl]carbamate

25

The carboxylic acid 56 (380 mg, 1.0 mmol) and <u>N</u>,<u>N</u>'-dicyclohexylcarbodiimide (230 mg, 1.1 mmol) and pentafluorophenol (200 mg, 1.1 mmol) were suspended in EtOAC (25 mL) and stirred for 2 hours then treated with (S)-2-amino-3-phenyl-1-propanol (150 mg, 1.0 mmol) and stirred at 40°C for 18 hours. The mixture was filtered and the filtrate was washed with sat aqueous citric acid followed by <u>sat aq NaHCO$_3$</u>

30

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followed by H_2O. The organic layer was dried (MgSO_4),
filtered, concentrated in vacuo and purified by
reverse-phase silica gel chromatography (LiChroprep®
RP-18) using MeOH:H_2O (4:1) as eluant to give the

5   product 6 (0.36 g, 71%); $[\alpha]_D^{20}$ = 20.4° (c = 0.25,
CH_2Cl_2); NMR (CDCl_3) δ 1.8 (14H, m), 2.60 (2H, d); 3.30
(4H, m), 4.05 (1H, m), 4.42 (1H, q, J), 4.78 (1H, m),
5.45 (1H, br s), 6.15 (1H, br s), 7.30 (8H, m), 7.37
(1H, d, J), 7.67 (1H, d), 8.25 (1H, br s).

10   Hydroxyamide (6) (See Scheme 22) (517 mg,
1.00 mmol), imidazole (146 mg, 2.15 mmol), and
tertiarybutyldimethylsilyl chloride (354 mg,
2.35 mmol) in DMF (6 mL) were stirred at room
temperature for 18 hours. The reaction was quenched

15   with H_2O (40 mL). The emulsion was extracted with
ether (80 mL). The ether was washed with brine, dried
(MGSO_4), filtered and concentrated in vacuo. The
crude material was purified by column chromatography
[SiO_2:hexane-ethyl acetate (2:1) as eluant] to give

20   the silyl protected amide (474 mg, 75%) as a white
foam. ^{1}H NMR (CDCl_3) δ 8.12 (1H, s, indNH), 7.76 (1H,
d, J 7 Hz, ind H-4), 7.40 (1H, d, J 8 Hz, ind H-7),
7.34-7.06 (8H, m, Ph+ind H-2, H-5, H-6), 6.98 (1H, s),
5.91 (6H, br s, NH?), 5.44 (0.4H, br s, NH?), 4.90

25   (1H, s, adamantyl H-2), 4.53 (1H, m, NHCH(CH_2ind)CO),
4.14 (1H, m, NHCH(CH_2OSi)CH_2Ph), 3,39 (2H, m, CH_2ind),
3.22 (2H, br, m, CH_2Ph), 2.12-1.54 (14H, br, m,
adamantyl), 0.88 (2, 9H, [t]Bu), 0.02 (6H, s, 2 x CH_3);
IR (film) vmax 2927 + 2856 (adamantyl), 1703 (CO

30   urethane), 1663 cm^{-1} (CO amide).

             Silyl protected amide (418 mg, 0.664 mmol) and
Lawesson's reagent [Aldrich] (268 mg, 0.663 mmol) were
refluxed in toluene (10 mL) for 30 minutes. The
solution was cooled to room temperature and poured

35   onto a column of silica gel. The column was eluted

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with CH$_2$Cl$_2$ to remove the toluene and a high rf (0.74)
Lawesson's reagent by-product. Elution was then
continued with a hexane-ethyl acetate gradient (0-30%)
to give thiazolene (9) (73 mg, 21%) as a white foam.

5   M.p. 56-63°C. ^{1}H NMR (CDCl$_3$) δ 8.16 (1H, s, ind NH),
7.63 (1H, d, J 8 Hz, ind H-4), 7.38-6.96 (9H, m, ind
H-7, H-6, H-5, H-2 + Ph), 5.44 (1H, br, d, J 7 Hz,
urethane NH), 4.88 (1H, br s, ind CH$_2$CH), 4.82 (1H, s,
adamantyl H-2), 4.62 (1H, m, NCHCH$_2$Ph), 3.44-2.83 (5H,

10 m, ind CH$_2$ + PhCH$_2$ + CH of CH$_2$S), 2.68 (1H, dd, J 9,
14 Hz, CH of CH$_2$S), 2.09-1.43 (14H, m, adamantyl); IR
(film) vmax 2909 + 2854 (adamantyl), 1698 (CO
urethane), 1621 cm^{-1} (C = N); MS (M/e;
Analysis for C$_{31}$H$_{35}$N$_3$SO$_2$:

15 Calc.: C, 72.48; H, 6.87; N, 8.18; S, 6.24%
Found: C, 72.32; H, 7.09; N, 7.75; S, 6.09%

EXAMPLE 94

(1-Phenylcyclopentyl)methyl[1S-[1R*(R*),2R*]] and [1S-
[1R*(S*),2R*]]-[2-[[2-hydroxy-1-(hydroxymethyl)-2-
20 phenylethyl]amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-
oxoethyl]carbamate

(1-Phenylcyclopentyl)methyl carbonochloroidate

Step A. To a stirred solution of 1-phenyl
cyclopentylmethanol (0.53 g, 3.0 mmol) in methylene
25 chloride (15 mL) was added bis (trichloromethyl)
carbonate (0.33 g, 1.1 mmol) followed by pyridine
(0.24 g, 3.3 mmol) in methylene chloride at 0°C. The
reaction mixture was warmed to room temperature and
stirred for an hour. The reaction mixture was
30 concentrated and diluted with ethyl acetate (25 mL).
The pyridinium hydrochloride precipitate was filtered
off and filtrate was concentrated to give semisolid
(0.65 g, 90%), ^{1}H NMR (200 MHz, CDCl$_3$) δ 7.50-7.10

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(5H, m), 4.30 (2H, s), 2.10-1.90 (4H, m), 1.90-1.75 (4H, m).

α-Methyl-N-[[(1-phenylcyclopentyl)methyl]carbonyl]-DL-tryptophan methyl ester

Step B. To a stirred solution of 1-phenyl 1-cyclopentyl methylchloroformate (0.65 g, 2.75 mmol) in dry THF (10 mL) was added a solution of α-methyl-DL-tryptophan methyl ester (0.60 g, 2.5 mmol) followed by triethylamine (0.5 g, 5.0 mmol) in dry THF. The reaction mixture was stirred for 30 minutes and then filtered, concentrated and chromatographed to give an oil (0.9 g, 90%). ^{1}H NMR (200 MHz, CDCl$_3$) δ 8.0 (1H, br s), 7.50 (1H, d, $\underline{J}$ 7 Hz), 7.40-7.0 (8H, m), 6.6 (1H, br s), 5.35 (1H, br s), 4.15 (2H, s), 3.65 (3H, s), 3.6-3.0 (2H, m), 2.10-1.85 (4H, m), 1.85-1.60 (4H, m), 1.55 (3H, s).

α-Methyl-N-[[(1-phenylcyclopentyl)methyl]carbonyl]-DL-tryptophan

Step C. To a stirred solution of intermediate B (0.87 g, 2 mmol) in aqueous 1,4-Dioxane (1:2) (6 mL) was added LiOH (0.13 g, 3 mmol) and stirred at room temperature overnight. The reaction mixture is concentrated, diluted with water (50 mL), acidified with dilute HCl, extracted with ethyl acetate and chromatographed to give a white foam (0.8 g, 95%). ^{1}H NMR (200 MHz, CDCl$_3$), 8.05 (1H, br s), 7.55 (1H, d, $\underline{J}$ 7 Hz), 7.45-7.00 (9H, m), 5.25 (1H, br s), 4.20-3.90 (2H, s), 3.35-3.05 (2H, m), 2.00-1.85 (4H, m), 1.85-1.65 (4H, m), 1.50 (3H, br s).

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(1-Phenylcyclopentyl)methyl[1S-[1R*(R*),2R*]] and [1S-
[1R*(S*),2R*]]-[2-[[2-hydroxy-1-(hydroxymethyl)-2-
phenylethyl]amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-
oxoethyl]carbamate

Step D. A solution of intermediate C (0.42 g,
1.0 mmol) in ethyl acetate (10 mL) was treated with
dicyclohexylcarbodiimide (0.23 g, 1.1 mmol) and
1-hydroxybenzotriazole hydrate (0.17 g, 1.1 mmol).
After stirring for an hour at room temperature, it was
filtered. To this filtrate, 2-amino-1-phenyl-1,3-
propanediol (0.18 g, 1.05 mmol) in 1:1 mixture of
methylene chloride and ethyl acetate was added and
stirred overnight. The reaction mixture was filtered,
concentrated and chromatographed to yield (0.25 g,
44%) of the title compound as a white foam.
m.p. 78-83°C.

EXAMPLE 95

(4-Nitrophenyl)methyl [4S-[4α,5α(R*)]] and [4S-
[4α,5α(S*)]]-[2-[(2,2-dimethyl-4-phenyl-1,3-dioxan-5-
yl)amino]-1-(1H-indol-3-ylmethyl-1-methyl-2-oxoethyl]-
carbamate

α-Methyl-N-[[(4-nitrophenyl)methoxy]carbonyl]-DL-
tryptophan methyl ester

Step A. The method was as described in Step B,
Example 94, except p-nitro benzyl chloroformate was
used. The title compound was obtained as a semisolid
(2.5 g, 49%). ^{1}HNMR (250 MHz, CDCl$_3$) δ 8.20 (2H, d, $\underline{J}$
8.5 Hz), 8.10 (1H, br s), 7.60-6.80 (7H, m), 5.64 (1H,
br s), 5.2-5.0 (2H, m), 3.71 (3H, s), 3.55 (1H, d, $\underline{J}$
14 Hz), 3.35 (1H, d, $\underline{J}$ 14 Hz), 1.72 (3H, s).

α-Methyl-N-[[(4-nitrophenyl)methoxy]carbonyl]-DL-
tryptophan

Step B.. The method was as described in Step C,
Example 94, except the product of Step A was used.
The title compound was obtained as a foam (1.8 g,
75%). ^{1}HNMR (250 MHz, CDCl$_3$) δ 8.15-7.95 (3H, m),
7.60-6.9 (7H, m), 5.53 (1H, br s), 5.20 (2H, s), 3.60-
3.20 (2H, m), 1.73 (3H, br s).

(4-Nitrophenyl)methyl [4S-[4α,5α(R*)]] and [4S-
[4α,5α(S*)]]-[2-[(2,2-dimethyl-4-phenyl-1,3-dioxan-5-
yl)amino]-1-(1H-indol-3-ylmethyl-1-methyl-2-
oxoethyl]carbamate

Step C. The method was as described in Step D,
Example 94, except the product of Step B and 5-amino-
2,2-dimethyl-4-phenyl-1,3-dioxan instead of the
product of Step C and 2-amino-1-phenyl-1,3-
propanediol, respectively. The title compound was
obtained as a foam (2.3 g, 85%). m.p. 92-102°C.

                          EXAMPLE 96

[4S-[4α,5α(R*)]] and [4S-[4α,5α(S*)]]-N-(2,2-dimethyl-
4-phenyl-1,3-dioxan-5-yl)-α-methyl-α-[[[(1-phenyl-
cyclopentyl)methyl]amino]carbonyl]-1H-indole-3-
propanamide

[4S-[4α,5α(R*)]] and [4S-[4α,5α(S*)]]-α-amino-N-(2,2-
dimethyl-4-phenyl-1,3-dioxan-5-yl)-α-methyl-1H-indole-
3-propanamide

Step A. A solution of the title compound of
Example 95 (1.65 g, 2.8 mmol) in absolute ethanol was
treated with catalytic amount of 10% palladium on
carbon and stirred overnight under a positive pressure
of hydrogen. The reaction mixture was then filtered
over celite and washed with ethanol. The filtrate was

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concentrated and passed through small plug of silica gel to give a white foam (1.1 g, 100%). m.p. 182-185°C.

[4S-[4α,5α(R*)]] and [4S-[4α,5α(S*)]]-N-(2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-α-methyl-α-[[[[(1-phenyl-cyclopentyl)methyl]amino]carbonyl]-1H-indole-3-propanamide

Step B. To a stirred solution of the product of Step A (0.49 g, 1.2 mmol) in dry THF (15 mL), was added 1-phenyl cyclopentylmethylisocyanate (0.26 g, 1.3 mmol) in dry THF (5 mL) at room temperature. The reaction mixture was concentrated, chromatographed and crystallized to give the title compound (0.21 g, 30%), m.p. 125-28°C.

EXAMPLE 97

[1S-[1R*(R*),2R*]] and [1S-[1R*(S*),2R*]]-N-[2-hydroxy-1-(hydroxymethyl)-2-phenyl ethyl]-2-(1H-indol-3-ylmethyl)-2-methyl-N[1] tricyclo[3.3.1.1[3,7]]dec-2-ylpropanediamide

N,N,N-Trimethyl-1H-indole-3-methanaminium iodide Gramine methiodide (2) (JACS 66 200 (1944))

Gramine (1) (43.5 g, 0.29 mmol) (see Synthetic Scheme 23 for Compounds 1-23) was dissolved in absolute ethanol (200 mL) and methyl iodide (17 mL, 0.27 mmol) was added dropwise over 0.5 hour. A mild exotherm occurred with the formation of a white precipitate. The reaction mixture was stirred overnight at room temperature and then cooled to 0°C for 2 hours. The white solid was collected by filtration, washed four times with ethanol (50 mL), three times with diethyl ether (50 mL), and dried in vacuo. The product was obtained as a white solid.

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70.4 g (83%).   IR (KBr) 3306, 1483, 1346, 810,
760 cm $^{-1}$.

Diethyl(1H-indol-3-ylmethyl)methylpropanedioate (3)

        Sodium hydride (4.0 g, 0.1 mmol) was added in
5   portions over 10 minutes to a mixture of diethylmethyl
        malonate (17.4 g, 0.1 mmol) in DMF (200 mL) at room
        temperature.   The reaction mixture was stirred
        5-minutes and gramine methiodide (33.5 g, 0.11 mmol)
        was added and the whole mixture warmed to 50°C for
10   0.5 hour and was then stirred overnight at room
        temperature.   Water (200 mL) was carefully added to
        quench the reaction.   The entire mixture was diluted
        with diethyl ether (500 mL) and water (300 mL).   The
        layers were separated and the organic layer was washed
15   with water (3 x 200 mL).   The combined aqueous layers
        were extracted with diethyl ether (1 x 500 mL), the
        ether layer washed with water, the organic extracts
        combined, dried (MgSO$_4$), filtered and concentrated.
        The residue was filtered through silica gel
20   (70-230 mesh) using hexane/ethyl acetate, 1/1, as
        eluant.   The product containing fractions were
        combined, concentrated, and filtered through silica
        gel (70-230) using 8/2 hexane/EtOAC as eluant.   The
        product was obtained as a red viscous oil.   13.1 g
25   (43%).   IR (film) 3397, 2983, 1731, 1376, 1254,
        1108 cm^{-1}.

Ethyl hydrogen(1H-indol-3-ylmethyl)-methylpropane-
dioate (4)

        To a solution of diester (4.85 g, 0.016 mmol) in
30   95% ethanol (50 mL) at room temperature was added 1N
        aqueous sodium hydroxide solution (16 mL) and enough
        water until the solution just became cloudy.   Water
        was added as the reaction proceeded.   After 2 hours

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the reaction mixture was concentrated on the rotary
evaporator to remove ethanol, diluted with water,
washed with ethyl acetate, made acidic with 10% citric
acid solution, brine was added, and the entire mixture
5   extracted with ethyl acetate. The ethyl acetate
solution was dried (MgSO$_4$), filtered and concentrated
to a brown oil. The brown oil was chromatographed on
silica gel (70-230 mesh) using ethyl acetate as eluant
and then rechromatographed on silica gel (70-230 mesh)
10   using hexane/ethyl acetate, 1/1, as eluant. The
product 4 was obtained as an orange/tan oil. 2.92 g
(66%) IR (film) 3402, 2982, 1718, 1458, 1098,
742 cm^{-1}.

Ethyl (±)-α-methyl-α-[(tricyclo[3,3,1.1^{3,7}]dec-2-
15   ylamino)carbonyl]-1H-indole-3-propanoate (5)
     A mixture of acid (1.41 g, 0.005 mmol),
adamantanamine hydrochloride (0.95 g, 0.005 mmol) 1-
hydroxybenzotriazole·H$_2$O (0.68 g, 0.005 mmol), and
CH$_2$Cl$_2$ (50 mL) was cooled to 0°C and triethylamine
20   (0.8 mL, 0.0057 mmol) was added and the mixture
stirred 5 minutes. Then dicyclohexylcarbodiimide
(1.04 g, 0.005 mmol) was added all at once. The
reaction mixture was stirred 3 days at room
temperature, concentrated to dryness, the residue
25   taken up in ethyl acetate, washed with 10% citric
acid, sodium carbonate and sodium chloride solutions.
The organic layer was dried (MgSO$_4$), filtered, and
concentrated to an orange oil. Addition of 1/1,
hexane/ethyl acetate caused the oil to solidify. The
30   solid was collected by filtration. 2.05 g (98%). IR
(KBr) 3418, 3327, 2907, 1713, 1630, 1540, 1457,
1113 cm^{-1}.

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(±)-α-methyl-α-[(tricyclo[3.3.1.1^{3,7}]dec-2-
ylamino)carbonyl]-1H-indole-3-propanoic acid (6)

The ester (1.04 g, 2.5 mmol) was dissolved in
ethanol (10 mL) and 1N sodium hydroxide solution
5   (3.5 mL) was added and just enough water to make the
solution cloudy. The reaction mixture was briefly
warmed to 50°C to get solution. The reaction mixture
was allowed to sit 14 days at room temperature. The
reaction mixture was concentrated to remove ethanol,
10   diluted with water, washed the aqueous solution with
ethyl acetate, made the aqueous layer acidic with 10%
citric acid solution, extracted with ethyl acetate,
washed the ethyl acetate solution with brine, dried
(MgSO$_4$), filtered, and concentrated to an off-white
15   foam. The foam was filtered through silica gel
(70-230 mesh) using ethyl acetate as eluant. The
product was obtained as an off-whit solid. 0.87 g
(90%). IR (KBr) 3411, 2908, 1716, 1617, 1540,
740 cm^{-1}.

20   [4S-[4α,5α(R*)]] and [4S[4α,5α(S*)]]N-(2,2-dimethyl-4-
phenyl-1,3-dioxan-5-yl)-2-(1H-indol-3-ylmethyl)-2-
methyl-N^1-(tricyclo[3.3.1.1^{3,7}]dec-2-yl)propanediamide
(7)

Dicyclohexylcarbodiimide (0.30 g, 1.46 mmol) was
25   added to a mixture of (4S,5S)-(+)-5-amino-2,2-
dimethyl-4-phenyl-1,3-dioxane (0.31 g, 1.44 mmol),
acid (0.53 g, 1.39 mmol), and 1-hydroxybenzotriazole
(0.22 g, 1.63 mmol) in a mixture 10/1, CH$_2$Cl$_2$/DMF,
(30 mL) at 0°C. The reaction mixture was allowed to
30   sit 1 hour at 0°C and then 3 days at room temperature.
The reaction mixture was concentrated to dryness, the
residue taken up in ethyl acetate, the ethyl acetate
solution washed with saturated sodium chloride
solution, dried (MgSO$_4$), filtered and concentrated to

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an orange oil. The oil was purified by filtration through silica gel (70-230 mesh) using hexane/ethyl acetate, 7/3, as eluant. The product was obtained as a white solid. 0.247 g (31%). IR (KBr) 3341, 2910, 1665, 1508, 1201, 742 cm^{-1}.

[1S-[1R*(R*),2R*]] and [1S-[1R*(S*),2R*]]-N-[2-hydroxy-1-(hydroxymethyl)-2-phenyl ethyl]-2-(1H-indol-3-ylmethyl)-2-methyl-N^{1}tricyclo[3.3.1.1^{3,7}]dec-2-ylpropanediamide (8)

A mixture of the acetonide (0.16 g, 0.28 mmol), methanol (10 mL), and 1N HCl (1 mL) was allowed to sit at room temperature for 4 hours. The reaction mixture was concentrated to dryness without heating. Ethyl acetate was added, the ethyl acetate dried (MgSO$_4$), filtered, concentrated, and the residue chromatographed on silica gel (70-230 mesh) using ethyl acetate as eluant. The product was obtained as a white foam. 0.0727 g (49%).

EXAMPLE 98

[1S-[1R*(R*),2R*]] and [1S-[1R*(S*),2R*]]-N-[2-hydroxy-1-(hydroxymethyl)-2-phenylethyl]-2-(1H-indol-3-ylmethyl)-2-methyl-N'-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)propanediamide

Ethyl α-methyl-α-[[(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)amino]carbonyl]-1H-indole-3-propanoate (9)

Compound 9 was prepared from Compound 4 according to the procedure for Compound 5. The product was obtained as an off-white solid. 3.49 g (58%). IR (KBr) 3402, 3337, 2913, 2904, 1718, 1652, 1116 cm^{-1}.

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(±)α-methyl-α-[[(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-
amino]carbonyl]-1H-indole-3-propanoic acid (10)

   Compound 10 was prepared from Compound 9 according
to the procedure for Compound 6. The product was
5 obtained as a white solid. 1.95 g (71%) IR (KBr)
3440, 2912, 1713, 1652, 1621, 1189, 746 cm^{-1}.

[4S-[4α,5α(R*)]] and [4S-[4α,5α(S*)]]-N-(2,2-dimethyl-
4-phenyl-1,3-dioxan-5-yl)-2-(1H-indol-3-ylmethyl)-2-
methyl-N'-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl-
10 propanediamide (11)

   Compound 11 was prepared from Compound 10
according to the procedure for Compound 7. The
product was obtained as a white foam. 0.83 g, (72%).
IR (KBr) 3418, 2904, 1666, 1558, 1106 cm^{-1}.

15 [1S-[1R*(R*),2R*]] and [1S-[1R*(S*),2R*]]-N-[2-
hydroxy-1-(hydroxymethyl)-2-phenylethyl]-2-(1H-indol-
3-ylmethyl)-2-methyl-N'-(tricyclo[3.3.1.1^{3,7}]dec-1-
ylmethyl)propanediamide (12).

   Compound 12 was prepared from Compound 11
20 according to the procedure for Compound 8. The
product was obtained as a white foam. 0.2633 g (91%).
IR (KBr) 3341, 1652, 1588, 1544, 1477, 699 cm^{-1}.

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EXAMPLE 99

[1S-[1R*(R*),2R*]] and [1S-[1R*(S*),2R*]]α-[[[[2,6-
bis(1-methylethyl)phenyl]amino]carbonyl]amino]-N-[2-
hydroxy-1-(hydroxymethyl)-2-phenylethyl]-α-methyl-1H-
indole-3-propanamide

[4S-[4α,5α(R*)]] and [4S-[4α,5α(S*)]]-1,1-dimethyl-
ethyl[2-[(2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl)-
amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]-
carbamate (14)

Compound 14 was prepared according to the
procedure of Compound 7. The product was obtained as
a white foam. 4.70 g (98%). IR (KBr) 3413, 1707,
1663, 1507, 1501, 1458, 1168, 743 cm^{-1}.

[4S-[4α,5α(R*)]] and [4S-[4α,5α(S*)]]-α-amino-N-(2,2-
dimethyl-4-phenyl-1,3-dioxan-5-yl)-α-methyl-1H-indole-
3-propanamide (15)

Anhydrous hydrogen chloride gas was bubbled
through a solution of t-butyloxy carbonyl amine
14 (3.4 g, 6.7 mmol) in dichloromethane (80 mL) for
5 minutes. The reaction mixture was allowed to sit at
room temperature for 1 hour and was then poured into
saturated aqueous sodium bicarbonate solution. Sodium
chloride solution was added and the aqueous solution
as extracted two times with ethyl acetate. The
organic extracts were combined, dried (MgSO$_4$),
filtered and concentrated. The residue was filtered
through silica gel (70-230 mesh) using ethyl acetate
as eluant to give the product as an off-white solid.
2.18 g (80%). IR (KBr) 3356, 3244, 1646, 1514,
744 cm^{-1}.

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[4S-[4α,5α(R*)]] or [4S-[4α,5α(S*)]]-α-[[[[2,6-bid(1-
methylethyl)phenyl]amino]carbonyl]amino]-N-(2,2-
dimethyl-4-phenyl-1,3-dioxan-5-yl)-α-methyl-1H-indole-
3-propanamide (16a)

5   [4S-[4α,5α(R*)]] or [4S-[4α,5α(S*)]]-α-[[[[2,6-bis(1-
methylethyl)phenyl]amino]carbonyl]amino]-N-(2,2-
dimethyl-4-phenyl-1,3-dioxan-5-yl)-α-methyl-1H-indole-
3-propanamide (16b)

        A mixture of amine 15 (0.40 g, 1 mmol) and 2,6-
10   diisopropylphenyl isocyanate (0.23 g, 1.1 mmol) in
        ethyl acetate (30 mL) was heated briefly to achieve
        solution. The reaction mixture was allowed to sit
        2 days at room temperature. The reaction mixture was
        concentrated to a viscous oil, which was
15   chromatographed on silica gel (70-230 mesh) using
        ethyl acetate as eluant. The less polar diastereomer,
        16a, was obtained as a white solid. 0.2876 g. The
        more polar diastereomer, 16b, was obtained as a white
        solid. 0.2369 g. Total yield (87%). IR (Kbr) 3431,
20   2964, 1675, 1500, 1239, 741 cm^{-1}.

[1S-[1R*(R*),2R*]] and [1S-[1R*(S*),2R*]]α-[[[[2,6-
bis(1-methylethyl)phenyl]amino]carbonyl]amino]-N-[2-
hydroxy-1-(hydroxymethyl)-2-phenylethyl]-α-methyl-1H-
indole-3-propanamide (17a)

25   Compound 17a was prepared from 16a according to
        the procedure for Compound 8. The product was
        obtained as a white foam. 0.0893 g (48%). IR (KBr)
        3400, 3343, 1733, 1663, 1513, 742 cm^{-1}.

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EXAMPLE 100

[1S-[1R*(R*),2R*]] or [1S-[1R*(S),2R*]]α-[[[[2,6-
bis(1-methylethyl)phenyl]amino]carbonyl]amino]-N-[2-
hydroxy-1-(hydroxymethyl)-2-phenylethyl]-α-methyl-1H-
indole-3-propanamide (17b)

Compound 17b was prepared from 16b according to
the procedure for Compound 8. The product was
obtained as a white foam. 0.096 g (66%). IR (KBr)
3420, 3299, 1734, 1716, 1662, 1507, 1058 cm^{-1}.

EXAMPLE 101

N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-α-
methyl-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl-DL-
tryptophanamide

[4S-[4α,5α(R*)]] and [4S-[4α,5α(S*)]]-[2-[(2,2-
dimethyl-4-phenyl-1,3-dioxan-5-yl)amino]-1-(1H-indol-
3-ylmethyl)-1-methyl-2-oxoethyl]carbamate (18)

The amine 15 (0.4 g, 1 mmol) and
2,6-diisopropylphenyl chloroformate (0.51 g, 2 mmol)
were taken up in tetrahydrofuran (50 mL) and
triethylamine (0.34 mL, 2.4 mmol) was added. The
reaction mixture was stirred 5 days at room
temperature and then concentrated to dryness. The
residue was filtered through silica gel (70-230 mesh)
using hexane/ethyl acetate, 1/1, as eluant. The
product was obtained as a foam/solid. 0.395 g (66%).
IR (KBr) 3326, 1654, 1636, 1520, 1257, 742 cm^{-1}.

N-[N[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-α-
methyl-DL-tryptophan methyl ester (19)

Compound 19 was prepared from BOC-L-phenylalanine
and RS-α-Me tryptophan methyl ester according to the
procedure for Example 7. 4.74 g (99%). IR (KBr)
3408, 3353, 1734, 1696, 1617, 1507, 1457, 1165 cm^{-1}.

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α-methyl-N-L-phenylalanyl-DL, methylester,
monohydrochloride (20)

5   Anhydrous hydrogen chloride gas was bubbled
through a solution of 19 (1.50 g, 3.1 mmol) in
dichloromethane (50 mL) for 2 minutes at room
temperature. The reaction mixture was allowed to sit
overnight at room temperature. The solvent was
removed in vacuo. Ether was added twice and
concentrated. The residue was taken up in methanol
10   and then concentrated. Ether was added and then
removed on the rotary evaporator yielding the product
as a tan foam. 1.32 g (100%). IR KBr) 3403, 3396,
3343, 3231, 1734, 1684, 1677, 1498, 1216, 743 cm^{-1}.

N-[N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl]-α-
15   methyl-DL-tryptophyl (21)

          Compound 21 was prepared from 19 according to the
procedure for Compound 6. The product was obtained as
a white foam. 2.34 g (96%). IR (KBr) 3375, 1716,
1708, 1702, 1498, 1457, 1368, 1164, 743 cm^{-1}.

20   N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-α-
methyl-N-tricyclo[3.3.1.1^{3,7}]dec-2-yl-DL-
tryptophanamide (22)

          Compound 22 was prepared from 21 and
2-adamantamine according to the procedure for
25   Compound 7. The product was obtained as a white
solid. 0.585 g (38%). IR (KBr) 3411, 3333, 1696,
1672, 1653, 1519, 1165 cm^{-1}.

EXAMPLE 102

N-[N-[(tricyclo[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-L-
30   phenylalanyl]-DL-tryptophan, methylester (23)

          Compound 20 (1.25 g, 3.0 mmol) was added to
2-adamantyl chloroformate (0.70 g, 3.3 mmol) in THF

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(80 mL), then triethyl amine (0.9 mL, 6.5 mmol) was
added and the reaction mixture cooled to 0°C. After
0.5 hour the reaction mixture was concentrated to
dryness, the residue was dissolved in ethyl acetate.
The ethyl acetate solution was washed with 10% aqueous
citric acid and saturated sodium chloride solutions,
dried (MgSO₄), filtered and concentrated. The residue
was filtered through silica gel (70-230 mesh) using
hexane/ethyl acetate as eluant. The product was
obtained as a white foam. 1.12 g (67%). IR (KBr)
3342, 2912, 1672, 1663, 1507, 1361, 1254, 1101 cm^{-1}.

EXAMPLE 103
Tricyclo[3.3.1.1^{3,7}]dec-2-yl(±)-[2-[(3,4-dihydro-2H-1-
benzopyran-3-yl)amino]-1-(1H-indol-3-ylmethyl)-1-
methyl-2-oxoethyl]carbamate
A solution of 2-adamantyl oxycarbonyl·αmethyl, DL
tryptophane (0.79 g , 0.002 mmol) in ethyl acetate
(60 mL) was treated with dicyclohexylcarbodiimide
(0.495 g, 0.002 mmol) and 1-hydroxybenzotriazole
hydrate (0.3 g, 0.0023 mmol). After stirring for
2 hours at room temperature the precipitated
dicyclohexyl urea was removed by filtration. To the
clear filtrate was added 3,4-dihydro-2,4-1-benzopyran-
3-amine (0.37 g, 0.002 mmol). The reaction mixture
was stirred at room temperature overnight. The ethyl
acetate solution was washed with 5% citric acid, 5%
NdHCO₃ and brine. The organic phase was dried over
MgSO₄ and concentrated in vacuo to yield a white foam.
The product was chromatographed over silica using 50%
ethyl acetate, 50% hexane as eluant to give the title
compound (0.66 g, 61%).
Analysis for C₃₂H₃₇N₃O₄ ½H₂O MW 536.679;
Calc.: C, 71.61; H, 7.13; N, 7.82;
Found: C, 71.67; H, 6.93; N, 7.75.

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EXAMPLE 104

Tricyclo[3.3.1.1^{3,7}]dec-2-yl(±)-[1-(1H-indol-3-
ylmethyl)-1-methyl-2-oxo-2-[[(1,2,3,4-tetrahydro-1-
naphthalenyl)methyl]amino]carbamate

5   In a process analogous to Example 103 by
substituting 1,2,3,4-tetrahydro-1-naphthalene-
methenamine (0.32 g, 0.002 mmol) for 3,4-dihydro-2,4-
1-benzopyran-3-amine one obtains the title compound
(0.76 g, 69%).

10   Analysis for C$_{34}$H$_{41}$N$_3$O$_3$ ½H$_2$O MW 548.734:
Calc.:   C, 74.42; H, 7.71; N, 7.65;
Found: C, 74.27; H, 7.57; N, 7.36.

EXAMPLE 105

Tricyclo[3.3.1.1^{3,7}]dec-2-yl(±)-[1-(1H-indol-3-
15   ylmethyl)-1-methyl-2-oxo-2-[(9H-xanthen-9-ylmethyl)-
amino]ethyl]carbamate

       A solution of 2-adamantyl oxycarbonyl-α-methyl DL
tryptophane (0.79 g, 0.002 mmol) in methylene chloride
(60 mL) was treated with hydroxybenzothiazole hydrate
20   (0.3 g, 0.0022 mmol), 1-(2-dimethylamino propyl)-3
ethyl carbodiimide·HCl (0.38 g, 0.002 mmol) and
triethyl amine (0.202 g, 0.002 mmol). After stirring
at room temperature for 2 hours a solution of 3H-
xanthane-9-methenamine (0.495 g, 0.002 mmol) in
25   methylene chloride (10 mL) was added. The reaction
mixture was stirred at room temperature overnight.
The clear solution was concentrated in vacuo. The
resulting oil was taken up in ethyl acetate. The
ethyl acetate solution was washed with 1 NHCl,
30   saturated NdHCO$_3$ and brine. The organic phase was
dried over MgSO$_4$ and concentrate in vacuo to give a
white foam. the product was chromatographed over
silica using 50% ethyl acetate; 50% hexane as eluant
to give the title compound (0.72 g, 59%).

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Analysis for $C_{37}H_{39}N_3O_4 \cdot H_2O$ MW 607.761:

Calc.:   C, 73.13; H, 6.79; N, 6.91;

Found: C, 73.53; H, 6.80; N, 6.61.

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CLAIMS

1.   A compound of formula·
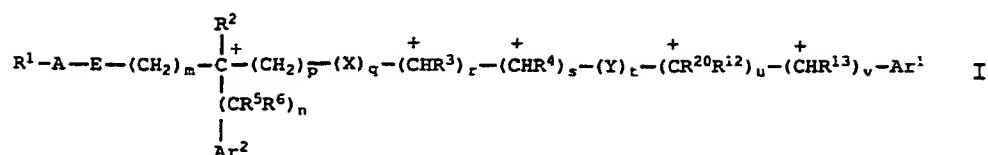
$$R^1-A-E-(CH_2)_m-\underset{\underset{Ar^2}{\overset{|}{(CR^5R^6)_n}}}{\overset{\overset{R^2}{|}}{\overset{+}{C}}}-(CH_2)_{\overline{p}}-(X)_q-(CHR^3)_r-(CHR^4)_s-(Y)_t-(CR^{20}R^{12})_u-(CHR^{13})_v-Ar^1 \qquad I$$

or a pharmaceutically acceptable salt thereof
wherein:

R^1 is a cyclo or polycycloalkyl hydrocarbon or
     mono- or polyheterocyclic moiety wherein the
     hetero atom(s) can be N, O, and/or S, of from
     3 to 12 carbon atoms with from 0 to
     4 substituents each independently selected
     from a straight or branched alkyl of from 1
     to 6 carbon atoms, halogen, CN, OR*, SR*,
     CO_2R^*, CF_3, NR^5R^6, or $(CH_2)_nOR^5$ wherein R*,
     R^5, and R^6 are each independently hydrogen or
     a straight or branched alkyl of from 1 to
     about 6 carbon atoms;

m, n, p, q, r, s, t, u, and v are each
     independently an integer of from 0 to 6 with
     the proviso that q, r, and s are not all 1
     when m, p, t, u, and v are all 0 except when
     X is not $CONR^9$ or A-E is not $(CH_2)_nCONH-$,
     $-SO_2NH-$, $-S(O)NH-$, $-NHCONH$, $-(CH_2)_n-OCO-NH-$,
     $-SCONH-$, $-O(CH_2)_nCO-$ or $-HC=CHCONH-$ wherein n
     is as above,

A is a bond,
     O,
     S,
     NR*,

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$-(CH_2)_nCO-Z,$

$-SO_2-Z,$

30      $-SO-Z,$

$-S-Z,$

$-NHCO-Z,$

$$-(CH_2)_n-O\overset{\overset{O}{\|}}{C}-Z,$$

35

$-SCO-Z,$

$-O-(CH_2)_nCO-Z,$

$-HC{=}CHCO-Z,$

wherein Z is a bond, oxygen, sulphur, or

40      $-NR*-$ wherein $R*$ is as defined above;

E is a bond,

an amino acid residue,

$-(CHR^3)_r-,$

$-(CHR^3)_r-(CHR^4)_s-,$

45      $-CONH-,$

$-NHCO-,$

$-OCO-,$

$-COO-,$

$-CH_2N(R^3)-,$

50      $-CH_2O-,$

$-CH_2S-,$

$-C{=}C-,$

$$-\overset{\overset{S}{\|}}{C}-NR^3,$$

55

$-SO_2NR^3-,$

$-NR^3SO_2-,$

-NHCONH-
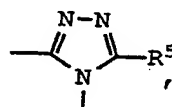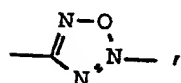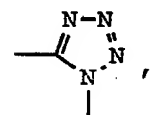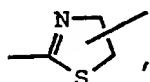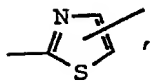
60

65   wherein r and s are independently as defined
     above and R^3 and R^4 are as defined above;
R^2 and R^{20} are each independently hydrogen, a
     straight or branched alkyl of from 1 to
     6 carbon atoms, $-HC=CH_2$, $-C\equiv CH$,
     $-(CH_2)_nCH=CH_2$, $-(CH_2)_nC\equiv CH$, $-(CH_2)_nAr^1$,

70      $-(CH_2)_nAr^2$, $-(CH_2)_nOR*$, $-(CH_2)_nOAr$,
     $-(CH_2)_nCO_2R*$, $-(CH_2)_nNR^5R^6$ wherein n, $R*$, R^5,
     and R^6 are as defined above, and Ar^1 and Ar^2
     are as defined below;
X and Y are each independently:

75      $-CONH-$,
     $-CONR^9$,
     $-NHCO-$,
     $-OCO-$,
     $-COO-$,

80      $-CH_2N(R^3)-$,

$-CH_2O-$,

$-CH_2S-$,

$-OCH_2-$,

$-SCH_2-$,

85       $-C=C-$,

$$-\overset{\overset{\textstyle S}{\|}}{C}-NR^3,$$

90       $$-NR_3-\overset{\overset{\textstyle S}{\|}}{C}-,$$

$-SO_2NR^3-$,

$-NR^3SO_2-$,

$-NHCONH-$,

95       $-CH(OR^*)CH_2-$,

$-COCH_2-$,

$-CH_2CO-$,

$-NR^3CH_2-$,

100

, or

;

wherein Q is O, S, or NR^9;

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R^3 and R^4 are each independently the same as R^2 or $-(CH_2)_{n'}-B-D$ wherein n' is an integer of from 0 to 3;

B is a bond,

$-OCO(CH_2)_n-$,

$-O(CH_2)_n-$,

$-NHCO(CH_2)_n-$,

$-CONH(CH_2)_n-$,

$-NHCOCH=CH-$,

$-COO(CH_2)_n-$,

$-CO(CH_2)_n-$,

$-SO(CH_2)_n-$,

$-S(CH_2)_n-$,

$-SO_2(CH_2)_n-$,

$$NHCO-\underset{\underset{R^7}{|}}{C}=\underset{\underset{R^8}{|}}{C}-,$$

$$NHCO-\overset{\overset{H}{|}}{\underset{\underset{R^7}{|}}{C}}-\overset{\overset{H}{|}}{\underset{\underset{R^8}{|}}{C}}-,$$

$$CONH-\underset{\underset{R^7}{|}}{C}=\underset{\underset{R^8}{|}}{C}-, \text{ or}$$

$$CONH-\overset{\overset{H}{|}}{\underset{\underset{R^7}{|}}{C}}-\overset{\overset{H}{|}}{\underset{\underset{R^8}{|}}{C}}-,$$

wherein R^7 and R^8 are each independently selected from hydrogen and R^2 or together form a ring $(CH_2)_m$ wherein m is an integer of from 1 to 5,

D is $-COOR*$,

$-CH_2OR*$,

$-CHR^2OR*$,

$-CH_2SR*$,

$-CHR^2SR*$,

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-CONR^{5}R^6,
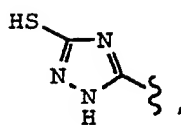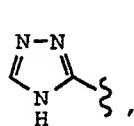
145

-CN,

-NR^{5}R^6,

-OH,

-H, and acid replacements such as

    tetrazole;

R^{10} is OH, NH$_2$, CH$_3$, or Cl

HO$_3$S-

-PO$_3$H$_2$

1,2,4 oxadiazole
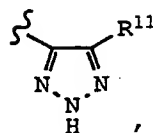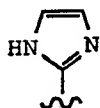
R^{11} is CN, CO$_2$H, or CF$_3$
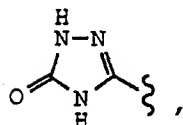
PhSO$_2$NHCO-,

CF$_3$CONHCO-,

CF$_3$SO$_2$NHCO-,

H$_2$NSO$_2$-,
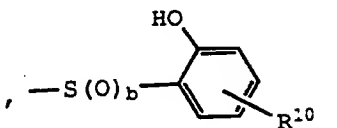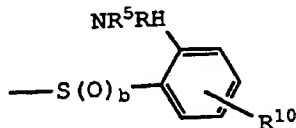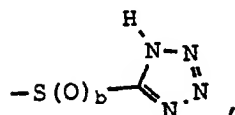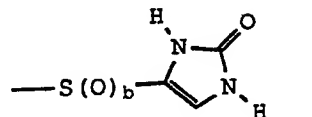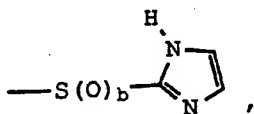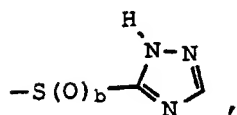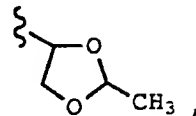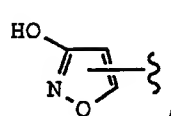
-202-

150   wherein b is an integer of from 0 to 2,
     wherein R*, R^2, R^5, and R^6 are as defined above;
     R^9 is H, or a straight or branched alkyl of from
     one to six carbon atoms, $-(CH_2)_nCO_2R*$, $(CH_2)_nOAr'$,
     $(CH_2)_nAr'$, $(CH_2)_nNR^5R^6$, wherein n, R*, R^5, and R^6

155 are as defined above or taken from R^3 and Ar is
     taken from Ar^1 as defined below;
          R^{12} and R^{13} are each independently hydrogen
     or taken together form a double bond, or are -
     $(CH_2)_n$-B-D as defined above; and

160   Ar^1 and Ar^2 are each independently a mono- or
     polycyclic unsubstituted or substituted carbo- or
     heterocyclic aromatic or carbo- or heteroaromatic
     moiety.

     2.   A compound according to Claim 1 wherein
          Ar^1 is phenyl,
               substituted phenyl,
               fused aryl,
     5   heterocycle,
               fused heterocycle, or
               perhydroaryl.

     3.   A compound according to Claim 1 wherein Ar^1 is
               2- or 3-thienyl,
               2- or 3-furanyl,
               2-, 3-, or 4-pyridinyl,
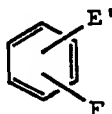
     5   wherein E' and F are each independently
          hydrogen, fluorine, chlorine, bromine,
          iodine, methyl, methoxy, trifluoromethyl,

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nitro, hydroxy, NH_2, OCF_3, and R^3 as defined above.

4. A compound according to Claim 1 wherein the polycycloalkyl is selected from the group consisting of
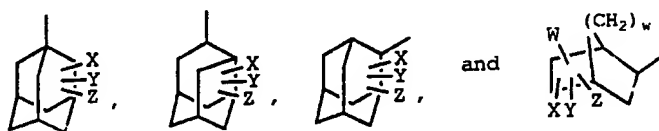

wherein W, X, Y, and Z are each independently hydrogen, a straight or branched alkyl of from one to six carbon atoms, CF_3, NR^5R^6, $-(CH_2)_nCO_2R^*$, CN, F, Cl, Br, OR^*, SR^*, wherein R^*, R^5, and R^6 are as defined in Claim 1 and w is an integer of from 1 to 3.

5. A compound according to Claim 1 named:
        Carbamic acid, [2-[[1-(hydroxymethyl)-2-phenylethyl]amino]-1-(1H-indol-3-ylmethyl)ethyl]-, tricyclo[3.3.1.1^{3,7}]dec-2-yl ester, [S-(R*,S*)]-,
        Carbamic acid, [2-[[1-(hydroxymethyl)-2-phenylethyl]amino]-1-(1H-indol-3-ylmethyl)ethyl-, tricyclo[3.3.1.1^{3,7}]dec-2-yl ester, [S-(R*,R*)]-,
        Tricyclo[3.3.1.1^{3,7}]dec-2-yl[1-[[[1-hydroxy-methyl)-2-phenylethyl]carbonyl]amino]-2-(1H-indol-3-yl)ethyl]carbamate,
        Carbamic acid, [2-[(2-hydroxy-2-phenylethyl)-amino]-1-(1H-indol-3-ylmethyl)-1-methylethyl]-, tricyclo[3.3.1.1^{3,7}]dec-2-yl ester (hydroxy center is RS, other center is R),

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15   Carbamic acid, [2-[[1-(hydroxymethyl)-2-
phenyl-ethyl]amino]-1-(1H-indol-3-ylmethyl)-1-
methylethyl]-, tricyclo[3.3.1.1^{3,7}]dec-2-yl ester,
[R-(R*,S*)]-, 4-methylbenzenesulfonate (1:1)
(salt),

20   Benzenepropanol,ß-[[2-(1H-indol-3-yl)-2-
[[(tricyclo[3.3.1.1^{3,7}]dec-2-
yloxy)carbonyl]amino]-propyl]amino]-, acetate
(ester), [R-(R*,S*)]-, 4-methylbenzenesulfonate
(1:1) (salt),

25   Carbamic acid, [[2-[acetyl[1-(hydroxymethyl)-
2-phenylethyl]amino]-1-(1H-indol-3-ylmethyl)-1-
methyl]ethyl]-, tricyclo[3.3.1.1^{3,7}]dec-2-yl
ester, [R-(R*,S*)]-,

          5,13-Dioxa-2,8-diazatetradec-10-enoic acid,
30   3-(1H-indol-3-ylmethyl)-3-methyl-4,9,12-trioxo-7-
phenyl-, tricyclo[3.3.1.1^{3,7}]dec-2-yl ester,
[S-(R*,S*)]-,

          5,13-Dioxa-2,8-diazatetradecanoic acid,
3-(1H-indol-3-ylmethyl)-3-methyl-4,9,12-trioxo-7-
35   phenyl-, tricyclo[3.3.1.1^{3,7}]dec-2-yl ester,
[R-(R*,R*)]-,

          Carbamic acid, [1-(1H-indol-3-ylmethyl)-1-
methyl-2-[(1-oxo-4-phenylbutyl)amino]ethyl]-,
tricyclo[3.3.1.1^{3,7}]dec-2-yl ester (R)-,

40   Carbamic acid, [2-(benzoylamino)-1-(1H-indol-
3-ylmethyl)-1-methylethyl]-, tricyclo[3.3.1.1^{3,7}]-
dec-2-yl ester, (R)-,

          Carbamic acid, [1-(1H-indol-3-ylmethyl)-1-
methyl-2-[(1-oxo-3-phenylpropyl)amino]ethyl]-,
45   tricyclo[3.3.1.1^{3,7}]dec-2-yl ester, (R)-,

          Carbamic acid, [1-(1H-indol-3-ylmethyl)-1-
methyl-2-[(2-phenylacetyl)amino]ethyl]-, tricyclo-
[3.3.1.1^{3,7}]dec-2-yl ester, (R)-,

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Carbamic acid, [2-[[3-[[1-(hydroxymethyl)-2-
phenylethyl]amino]-3-oxopropyl]amino]-1-(1H-indol-
3-ylmethyl)-1-methyl-2-oxoethyl]-, [R,(R*,S*)]-,

50

Carbamic acid, [1-(1H-indol-3-ylmethyl)-2-
[[3-[[1-(hydroxymethyl)-2-phenylethyl]amino]-3-
oxopropyl]amino]-1-methyl-2-oxoethyl]-, tricyclo-
[3.3.1.1^{3,7}]dec-2-yl ester, [S-(R*,R*)]-,

55

D-Phenylalaninamide, α-methyl-N-[(tricyclo-
[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-D-tryptophyl-ß-
alanyl-,

L-Phenylalaninamide, α-methyl-N-[(tricyclo-
[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-D-tryptophyl-ß-
alanyl-,

60

L-Phenylalaninamide, α-methyl-N-[(tricyclo-
[3.3.11.1^{3,7}]dec-2-yloxy)carbonyl]-L-tryptophyl-ß-
alanyl-,

D-Phenylalaninamide, α-methyl-N-[tricyclo-
[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-L-tryptophyl-ß-
alanyl-,

65

12-Oxa-2,5,9-triazatridecanoic acid, 3-(1H-
indol-3-ylmethyl)-3-methyl-4,8,11-trioxo-10-
(phenylmethyl)-, tricyclo[3.3.1.1^{3,7}]dec-2-yl
ester, [R,(R*,R*)]-,

70

L-Phenylalanine, N-[N-[α-methyl-N-[(tricyclo-
[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-D-tryptophyl]-ß-
alanyl]-, phenylmethyl ester,

Propanoic acid, 2-[[3-[[3-(1H-indol-3-yl)-2-
methyl-1-oxo-2-[[(tricyclo[3.3.1.1^{3,7}]dec-2-
yloxy)carbonyl]amino]propyl]amino]-1-oxopropyl]-
amino]-3-phenyl-, phenylmethyl ester,
[S-(R*,R*)]-,

75

D-Phenylalanine, N-[N-[α-methyl-N-[(tricyclo-
[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-D-tryptophyl]-ß-
alanyl]-,

80

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L-Phenylalanine, N-[N-[α-methyl-N-[(tricyclo-
[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-D-tryptophyl]-ß-
85   alanyl]-,

L-Phenylalanine, N-[N-[α-methyl-N-[(tricyclo-
[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-L-tryptophyl]-ß-
alanyl]-,

Benzenepropanoic acid, α-[[3-[[3-[(1H-indol-
90   3-yl)-2-methyl-1-oxo-2-[[(tricyclo[3.3.1.1^{3,7}]dec-
2-yloxy)carbonyl]amino]propyl]amino]-1-oxopropyl]-
amino]-, [S-(R*,S*)]-,

Glycine, N-[2-methyl-N-[(tricyclo-
[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-D-tryptophyl]-,
95   phenylmethyl ester,

Carbamic acid, [3-(1H-indol-3-ylmethyl)-2,5-
dioxo-1-(2-phenylethyl)-3-pyrrolidinyl]-,
tricyclo[3.3.1.1^{3,7}]dec-2-yl ester, (±)-,

Carbamic acid, [1-(1H-imidazol-4-ylmethyl)-1-
100   methyl-2-oxo-2-[(2-phenylethyl)amino]ethyl]-, 1,1-
dimethylethyl ester, (±)-,

Carbamic acid, [3-(1H-indol-3-yl)-1-methyl-1-
[[(2-phenylethyl)amino]carbonyl]propyl]-,
tricyclo[3.3.1.1^{3,7}]dec-2-yl ester, (±)-,

105   Carbamic acid, [1-[[[1-hydroxymethyl)-2-
phenylethyl]amino]carbonyl]-3-(1H-indol-3-yl)-1-
methylpropyl]-, tricyclo[3.3.1.1^{3,7}]dec-2-yl ester
(hydroxymethyl center is S, other center is RS),

13-Oxa-2,5,ß-triazatetradec-10-enoic acid, 3-
110   [2-(1H-indol-3-yl)ethyl]-3-methyl-4,5,12-trioxo-7-
phenyl-, tricyclo[3.3.1.1^{3,7}]dec-2-yl ester [TRP
center is R/S mixture, other center is R],

L-Phenylalaninamide, N-[[(1,1-dimethyl-
ethoxy)-carbonyl]-α-methyl]-L-tryptophyl]-L-
115   methionyl-L-α-aspartyl-,

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Glycine, N-[2-methyl-N-[(tricyclo-
[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-D-tryptophyl]-L-
phenylalanyl-,

120

Carbamic acid, [1-[[[1-(hydroxymethyl)-2-
phenylethyl]amino]carbonyl]-2-(1H-indol-3-yl)-
propyl]-, tricyclo[3.3.1.1^{3,7}]dec-2-yl ester
(hydroxymethyl center S, other centers RS),

2,4-Heptadienoic acid, 6-[[3-(1H-indol-3-yl)-
2-methyl-1-oxo-2-[[(tricyclo[3.3.1.1^{3,7}]dec-2-

125

yloxy)carbonyl]amino]propyl]amino]-7-phenyl-,
[R,R*,S*-(E,E)]]-,

Glycine, N-[2-methyl-N-[(tricyclo-
[3.3.1.1^{3,7}]dec-2-yloxy)carbonyl]-D-tryptophyl]-,
phenylmethyl ester,

130

Tricyclo[3.3.1.1^{3,7}]dec-2-yl-R-(R*,S*)]-
[1-[4,5-dihydro-4-(phenylmethyl)-2-thiazolyl]-
2-(1H-indol-3-yl)-1-methylethyl]carbamate.

6. A pharmaceutical composition comprising an amount
of a compound according to Claim 1, effective to
suppress the appetite in a mammal, and a
pharmaceutically acceptable carrier.

7. A method of suppressing appetite in a mammal,
comprising administering an effective appetite
suppressing amount of a compound according to
Claim 1.

8. A pharmaceutical composition comprising an amount
of a compound according to Claim 1, effective to
reduce gastric acid secretion in a mammal, and a
pharmaceutically acceptable carrier.

9. A method of reducing gastric acid secretion in a
mammal, comprising administering an effective

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gastric acid secretion reducing amount of a
compound according to Claim 1.

10. A pharmaceutical composition comprising an amount
    of a compound according to Claim 1, effective to
    reduce anxiety in a mammal, and a pharmaceutically
    acceptable carrier.

11. A method of reducing anxiety in a mammal,
    comprising administering an effective anxiety
    reducing amount of a compound according to
    Claim 1.

12. A pharmaceutical composition comprising an amount
    of a compound according to Claim 1 effective to
    treat gastrointestinal ulcers in a mammal, and a
    pharmaceutically acceptable carrier.

13. A method for treating gastrointestinal ulcers in a
    mammal comprising administering an effective
    gastrointestinal ulcer treating amount of a
    compound according to Claim 1.

14. A pharmaceutical composition comprising an amount
    of a compound according to Claim 1 effective to
    treat psychotic behavior in a mammal, and a
    pharmaceutically acceptable carrier.

15. A method of treating psychosis in a mammal,
    comprising administering an effective psychosis
    treating amount of a compound according to
    Claim 1.

16. A pharmaceutical composition comprising an amount
    of a compound according to Claim 1 effective to

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block the reaction caused by withdrawal from drug
or alcohol use in a mammal, and a pharmaceutically

5   acceptable carrier.

17. A method of blocking drug or alcohol withdrawal
    reaction in a mammal comprising administering an
    effective withdrawal reaction blocking amount of a
    compound according to Claim 1.

18. A pharmaceutical composition comprising an amount
    of a compound according to Claim 1 effective to
    potentiate the effects of morphine and other
    opioids in treating pain.

19. A method of treating pain in a mammal, comprising
    administering an effective amount of a compound
    according to Claim 1.

20. A pharmaceutical composition comprising an amount
    of a compound according to Claim 1 effective to
    treat and/or prevent panic.

21. A method of treating and/or preventing panic in a
    mammal, comprising administering an effective
    amount of a compound according to Claim 1.

22. Method of use of a radioactive iodo compound of
    formula I to prepare a pharmaceutical or
    diagnostic composition for the treatment or
    diagnosis of gastrin-dependent tumors.

INTERNATIONAL SEARCH REPORT

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) 6

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): A61K 37/02; C07K 5/08, 5/10
U.S.Cl.: 530/330, 331; 514/18

II. FIELDS SEARCHED

Minimum Documentation Searched 7

Classification System	Classification Symbols
U.S.Cl.	530/330, 331; 514/18

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched 8

APS, BIOSIS, SEARCH TERMS: CCK ANTAGONISTS

III. DOCUMENTS CONSIDERED TO BE RELEVANT 9

Category *	Citation of Document, 11 with indication, where appropriate, of the relevant passages 12	Relevant to Claim No. 13
X Y	US,A, 4,757,157 (HORWELL), 12 JULY 1988, see entire document.	1-22 1-22
X Y	EP,A 0,227,173 (ABBOTT LABORATORIES) 11 OCTOBER 1989, see entire document.	1-22 1-22

* Special categories of cited documents: 10

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
25 November 1991	17 DEC 1991
International Searching Authority	Signature of Authorized Officer
ISA/US	S.G. Marshall